EDITORIAL BOARD

Editor-in-Chief
Giuseppe Argenziano, MD
Dermatology Unit,
University of Campania, Naples, Italy

Deputy Editor
Aimilios Lallas, MD
First Department of Dermatology,
Aristotle University, Thessaloniki, Greece

Associate Editors
Gabriella Brancaccio, MD
Dermatology Unit,
University of Campania, Naples, Italy
Stefano Cacavale, MD
Dermatology Unit,
University of Campania Luigi Vanvitelli, Naples, Italy
Michela Lai, MD
Department of Dermatology,
University of Modena and Reggio Emilia, Modena, Italy
Teresa Russo, MD
Dermatology Unit,
University of Campania, Naples, Italy

Founding Editor
A. Bernard Ackerman, MD

Social Media Manager
Ruzica Jurakic Toncic, MD
Department of Dermatovenereology,
University Hospital Centre Zagreb, Zagreb, Croatia

Allergology
Ruzica Jurakic Toncic, MD
Zagreb, Croatia

Autoimmune & Blistering Diseases
Vito Di Lernia, MD
Reggio Emilia, Italy

Confocal & Skin Imaging
Caterina Longo, MD
Modena, Italy
Marco Mannoni, MD
Modena, Italy

Cosmetic & Aesthetic Dermatology
Elisabetta Fulgione, MD
Naples, Italy
Camila Scharf, MD, MSc
Naples, Italy
Stefania Guida, MD
Modena, Italy

Dermato-Oncology
Giulia Briatico, MD
Naples, Italy
Elisa Moscarella, MD
Naples, Italy
Ahmed Sadek, PhD, MSc, DBA
Cairo, Egypt
Emi Dika, MD
Bologna, Italy
Gabriel Salerni, MD
Rosario, Argentina

Infectious Diseases & STDs
Enzo Errichetti, MD
Udine, Italy
Sonia Segura, MD
Barcelona, Spain

Inflammatory Diseases
Marco Ardigò, MD
Rome, Italy
Grazia Balboni, MD
Naples, Italy
Anna Balato, MD
Naples, Italy
Laura Calabrese, MD
Siena, Italy
Marco Galluzzo, MD
Rome, Italy

Pediatric Dermatology
Andrea Bassi, MD, PhD
Lucca, Italy
Vincenzo Piccolo, MD
Naples, Italy
Julia Nowowiejska, MD
Białystok, Poland

Statistics
Athanasios Kyrgidis, MD
Thessaloniki, Greece

Dermatologic Surgery
John Paoli, MD
Gothenburg, Sweden

Dermatopathology
Zoe Apalla, MD
Thessaloniki, Greece
Mattheos Bobos, MD
Thessaloniki, Greece

Dermoscopy
Bengu Nisa Akay, MD
Ankara, Turkey
Cristian Navarrete Dechent, MD
Santiago, Chile
Teresa Maria Kränke, MD
Graz, Austria
Konstantinos Liospyris, MD
Athens, Greece
Riccardo Pampena, MD
Reggio Emilia, Italy
Danica Todorovic, PhD, MD
Nis, Serbia

Hair & Nail Diseases
Michela Starace, MD
Bologna, Italy

Mattioli 1885
srl - Strada di Lodesana 649/sx
Loc. Vaio - 43036 Fidenza (Parma)
tel +39 0524 530383
fax +39 0524 82537
www.mattioli1885.com
E-mail: redazione@mattioli1885.com

Editorial Office
Rosa Poldi Allay
E-mail: email@dpcj.org
Evaluation of the Quality of Life and the Demographic and Clinical Characteristics of Patients With Pemphigus With Oral Mucosal Involvement: A Multicenter Observational Study


https://doi.org/10.5826/dpc.1402a99

“The severity of oral pemphigus vulgaris is correlated with a decline in quality of life measures. A marked decline in quality of life was noted among patients presenting with superficial ulcers, flaccid bullae, lesions measuring 1 cm or more in diameter.”

Efficacy of Low-Level Laser Versus Topical Erythromycin 2% in the Treatment of Inflammatory Acne Vulgaris

Samar Saeed Ashmawy, Elham Mohamed Kassem, Sherreen Farouk Gheida, Nahla Elsayed Ramzy

https://doi.org/10.5826/dpc.1402a48

“Low level laser and topical antibiotic efficacy in acne vulgaris treatment.”

Acquired Perforating Dermatosis: Clinical and Histopathological Analysis of 95 Patients From One Center

Yusuf Can Edeh, Yağmur Aypek, Betül Öğüt, Özlem Erdem, Esra Adişen

https://doi.org/10.5826/dpc.1402a100

“Acquired Perforating Dermatosis (APD) is a disease group characterized by transepidermal elimination of dermal connective tissue materials such as collagen, elastic fibers, and keratin through the epidermis and observed with pruritic skin lesions. APD is usually accompanied by systemic comorbidities. There are several topical and systemic medications available for APD, however, sometimes the therapy might be challenging.”

Combining Reflectance Confocal Microscopy, Optical Coherence Tomography, and Ex-Vivo Fluorescence Confocal Microscopy for Margin Assessment in Basal Cell Carcinoma Excision

Simone Michelinii, Victor Desmond Mondel, Marco Ardigò, Silvana Ciardo, Carlo Cola, Anna Maria Cesinara, Elena Rossi, Barbara Ferrari, Shaniko Kaleci, Marco Di Fraia, Camilla Chello, Carmen Cantisani, Federica Trovato, Caterina Longo, Giovanni Pellacani

https://doi.org/10.5826/dpc.1402a90

“Integration of noninvasive (RCM-OCT) and invasive FCM imaging enhances precise margin assessment in basal cell carcinomas, improving presurgical and intrasurgical tumor management for better outcomes.”

Dermoscopy of Actinic Lichen Planus in Skin of Color

Awatef Kelati, Asmae Rassa, Soumiya Chiheb

https://doi.org/10.5826/dpc.1402a101

“This study highlighted different dermoscopic patterns of various subtypes of Actinic Lichen Planus in skin of color, mainly the pigmented (melasma-like), annular, plaque-like, and dyschromic variants.”
Dermatitis Artefacta: A Retrospective Descriptive Study of 46 Patients
Eugenia Veronica Di Brizi, Gianluca Ficca, Vincenzo Piccolo, Camila Scharf, Giulia Briatica, Sebastiano Pellerone, Giuseppe Argenziano
https://doi.org/10.5826/dpc.1402a45

"Self-induced dermatoses are self-inflicted skin lesions, for which the patient denies responsibility and often underlie psychiatric disorders. A complete psychiatric evaluation is certainly necessary to clarify the diagnosis and define the correct therapeutic intervention."

Correlation of Specific Inflammatory Markers With the Occurrence of Depression in Patients With Psoriasis and Their Use as Biomarkers for the Diagnosis Of Depression
Eleni Mitsiou, Aikaterini Kyriakou, Eleni Parlapani, Anastasia Trigoni, Myrto Trakatelli, Zoe Apalla, Dimitrios Sotiriadis, Elizabeh Lazaridou, Aikaterini Patsatsi
https://doi.org/10.5826/dpc.1402a104

"Psoriasis is a systemic disease associated with a wide range of comorbidities. The study aimed to examine a potential association between inflammatory markers and depression in patients with psoriasis."

Intralesional Quadrivalent Human Papillomavirus Vaccine Versus Candida Antigen in the Treatment of Multiple Recalcitrant Non-Genital Warts
Ibrahim Fouda, Hassan Abou Khodair Mohammed, Ghada Mohammed Youssef Mohammed
https://doi.org/10.5826/dpc.1402a66

"Intralesional antigen immunotherapy is a potentially effective treatment method for different types of warts. Intralesional quadrivalent HPV vaccine was superior to candida antigen in treatment of non-genital warts."

Serum Levels of IL-35, One of the Newest Members of the 2003-2014 National Inpatient Sample
Vrusha Shah, Amar Desai, Shari Lipner
https://doi.org/10.5826/dpc.1402a34

"The association between the characteristics of vitiligo and serum levels of IL-35 cytokine family and the differences of serum levels between Vitiligo patients and healthy controls suggests that IL-35 cytokine family may play a role in the pathogenesis of vitiligo."

Dermoscopy of Pigmented Bowen Disease: A Multicenter Study on Behalf of the Ibero-Latin American College of Dermatology (CILAD)
https://doi.org/10.5826/dpc.1402a69

"Pigmented structures and the clues derived from the presence of melanin are much more frequent in patients skin phenotype 3 and 4 than in fair skin."

Real-World Experience of Tofacitinib and Baricitinib Use in Alopecia Areata in Greek Population: A Retrospective Analysis With Focus on Safety
Zoe Apolla
https://doi.org/10.5826/dpc.1402a73

"Our study showed efficacy and safety of JAK inhibitors in alopecia areata patients, treated in real-life settings. Efficacy was not influenced by age group, clinical type, or by time since the last episode of AA, whilst tolerability was optimal in younger individuals."

Triamcinolone Injection in the Treatment of Malar Edema
Wioletta Barariska-Rybala, Zuzanna Swierczewska, Agnieszka Lemiec, Lee Walker
https://doi.org/10.5826/dpc.1402a117

"Given the nature of malar edema, its management remains problematic. The most commonly reported treatment modality is injection with hyaluronidase nonetheless, it has not proven to be effective in all cases thus, new therapeutic options are emerging. Here, we aimed to determine the safety and efficacy of triamcinolone injection in the treatment of malar edema."

Dermatology Quality of Life and Depression Anxiety and Stress-42 Scale in Scabies Patients
Serap Karadogan
https://doi.org/10.5826/dpc.1402a112

"Scabies may affect both quality of life and psychosocial health. All patients should be evaluated and consulted, if needed, for possible psychosocial problems as well as other secondary complications."

Impact of Vitiligo on Quality of Life in Patients of Skin of Color and Its Correlation With Clinical Severity Assessment Scores Using Disease Specific Scores: a Cross-Sectional Study
Guneet Awan Guneet Awan, Navleen Kaur, Guramrit Singh, Nishant Sharma
https://doi.org/10.5826/dpc.1402a75

"Disease specific QOL scores, together with their domains and graded scales are imperative in psychological evaluation and multidisciplinary management of patients as QOL in vitiligo is notably influenced by disease severity scores."

Retrospective Analysis of Onychomycosis Risk Factors Using Disease Specific Scores, together with their domains and graded scales are imperative in psychological evaluation and multidisciplinary management of patients as QOL in vitiligo is notably influenced by disease severity scores.

Contact Sensitivity of Turkish Children and Adolescents to European Baseline Series Allergens between 2013 and 2023
Vrusha Shah, Amar Desai, Shari Lipner
https://doi.org/10.5826/dpc.1402a374

"Onychomycosis patients commonly were Black and had greater hospital stays and costs. Comorbidity risk factors included tinea pedis, venous insufficiency, human immunodeficiency virus, psoriasis, obesity, peripheral vascular disease, and diabetes."

A Real-Life 208 Week Single-Centred, Register-Based Retrospective Study Assessing Secukinumab Survival and Long-Term Efficacy and Safety Among Greek Patients With Moderate to Severe Plaque Psoriasis, Including Difficult-to-Treat Manifestations Such as Genitals and Scalp
Eirini Kyrmanidou, Christina Kemanetzis, Chatzopoulos Stavros, Myro-Georgia Trakatelli, Aikaterini Patsatsi, Xenia Madi, Dimitra Ignatiadi, Evangelia Kalionidou, Zoe Apolla, Elizabeth Lazaridou
https://doi.org/10.5826/dpc.1402a351

"Secukinumab is an effective treatment choice for treating chronic plaque psoriasis, additionally it can be efficacious in the subgroups of patients with difficult-to-treat manifestations such as genitals and scalp."

"Given the nature of malar edema, its management remains problematic. The most commonly reported treatment modality is injection with hyaluronidase nonetheless, it has not proven to be effective in all cases thus, new therapeutic options are emerging. Here, we aimed to determine the safety and efficacy of triamcinolone injection in the treatment of malar edema."

"Scabies may affect both quality of life and psychosocial health. All patients should be evaluated and consulted, if needed, for possible psychosocial problems as well as other secondary complications."

"Disease specific QOL scores, together with their domains and graded scales are imperative in psychological evaluation and multidisciplinary management of patients as QOL in vitiligo is notably influenced by disease severity scores."

"Onychomycosis patients commonly were Black and had greater hospital stays and costs. Comorbidity risk factors included tinea pedis, venous insufficiency, human immunodeficiency virus, psoriasis, obesity, peripheral vascular disease, and diabetes."

"Metals and preservatives are main allergen groups in Turkish children. Nickel sensitivity in population would expect to decrease with Turkish legislations that limited nickel release and fully enforced by the end of 2021. Regulations are required to reduce the permitted level of Ni in rinse-off cosmetics."

"Our study showed efficacy and safety of JAK inhibitors in alopecia areata patients, treated in real-life settings. Efficacy was not influenced by age group, clinical type, or by time since the last episode of AA, whilst tolerability was optimal in younger individuals."
Efficacy of Long-Pulsed Nd:YAG Laser for Classic Kaposis Sarcoma: A Dermoscopic Study
Seher Bostanci, Merve Aygun Alizada, Banu Farabi, Bengu Nisa Altay
https://doi.org/10.5826/dpc.1402a150

“Long-pulsed Nd:YAG laser therapy may prove to be an effective therapeutic alternative for both early and advanced stages of classic Kaposis sarcoma, particularly in cases of recalcitrant skin lesions or in patients receiving systemic therapy. Long-pulsed Nd:YAG laser therapy may offer potential benefits to HIV-positive patients, as it is free of immunosuppression, easy to apply to recurrent lesions, and has demonstrated overall efficacy and safety.”

Bimekizumab for the Treatment of Plaque Psoriasis With Involvement of Genitalia: A 16-Week Multicenter Real-World Experience—IL-PSO (Italian Landscape Psoriasis)
Diego Orsini, Piergiorgio Malagoli, Anna Balata, Luca Bianchi, Pina Brianti, Dario Buonanato, Martina Burlando, Giacomo Calderarola, Anna Campanori, Elena Campione, Carlo G. Carrera, Andrea Carugno, Francesco Cusano, Paolo Dapavo, Annunziata Dattola, Clara De Simone, Valentina Dini, Maria Esposito, Maria C. Fargnoli, Francesca M. Gaiani, Luigi Gargiulo, Paolo Gisondi, Alessandro Giunta, Luciana Ibbi, Claudia Lasogni, Francesco Locosole, Vincenzo Maione, Edoardo Montalto, Angelo M. Marzano, Martina Morelli, Matteo Megna, Santa R. Mercuri, Alessandra Narcisi, Annamaria Offidani, Giovanni Poilini, Aurora Parodi, Giovanni Pellecacci, Luca Potestio, Pietro Quaglini, Antonio G. Richetta, Francesca Romano, Paolo Sena, Marina Venturini, Chiara Assorgi, Antonio Costanzo
https://doi.org/10.5826/dpc.1402a152

“In this retrospective multicenter study, bimekizumab showed rapid effectiveness in patients affected by genital psoriasis. The safety profile of bimekizumab was consistent with data from clinical trials.”

Long-Term Effectiveness of Brodalumab for the Treatment of Moderate-To-Severe Psoriasis: A Real-Life Multicenter Study of Up to 3 Years in a Real Life Italian Cohort
Giacomo Calderarola, Marco Galluzzo, Nicoletta Bernardini, Elisabetta Botti, Eleonora De Luca, Clara De Simone, Marco Mariani, Gaia Moretta, Sabatino Paillotta, Elena Campione, Keto Peris
https://doi.org/10.5826/dpc.1402a153

“Brodalumab has shown long-term effectiveness and safety in moderate-severe psoriasis for up to 3 years, with cumulative survival rates at weeks 52 and 104 of 86.32% and 78.03%, respectively.”

Photodynamic Therapy for the Treatment of Basal Cell Carcinoma: A Comprehensive Review of Randomized Controlled Trials
Ioannis-Alexios Kouprentziotis, Natalia Rompoti, Konstantinos Liopyris, Electra Nicolaidou, Alexander Stratigos
https://doi.org/10.5826/dpc.1402a105

“Many different randomized controlled trials have compared photodynamic therapy with other treatment modalities and have demonstrated that photodynamic therapy is a safe and efficacious option for the treatment of superficial basal cell carcinoma and to a lesser extent nodular basal cell carcinoma.”

Oral Diseases During Systemic Psoriatic Drugs: A Review of the Literature and Case Series
Annunziata Raimondo, Federica Di Spirito, Serena Lembo
https://doi.org/10.5826/dpc.1402a107

“This narrative review discusses on studies that describe oral adverse drug reactions in the context of systemic therapy for psoriasis.”

Efficacy of Intralosional Methotrexate Injection versus Triamcinolone Acetonide in Nail Psoriasis: A Systematic Review and Meta-Analysis
Stephanie Nathania, Diah Adriani Malih, Muslimin, Haridjan
https://doi.org/10.5826/dpc.1402a109

“ Intralosional injection therapy in nail psoriasis is a promising option. Both methotrexate and triamcinolone acetonide can be used and yield favorable outcomes.”

Tape Stripping — Searching for Minimally Invasive Biomarkers in Atopic Dermatitis
Weronika Zyskh, Magdalena Trzeciak
https://doi.org/10.5826/dpc.1402a123

“Stratum corneum samples collected by tape stripping provide a wide range of immune and epidermal barrier biomarkers. Although numerous potential biomarkers have been identified, none of these candidates have been validated and implemented into routine clinical practice yet.”

A Systematic Review of Diagnoses With Rosettes Under Dermoscopy
May Alorainy, Kendall Buchanan, Tyler Nussinow, Judy B. Robinowitz, Peggy Cyr, Elizabeth V. Seiverling
https://doi.org/10.5826/dpc.1402a125

“Rosettes are a dermoscopic finding seen in keratinocytic neoplasms. This systematic review shows that they are also observed in many other conditions. Comprehensive clinical evaluation is crucial for accurate diagnosis.”

Pilomatricoma: Clinical, Dermoscopic Findings and Management in 55 Pediatric Patients and Concise Review of the Literature With Special Emphasis on Dermoscopy
Marco Adriano Chessa, Maria Francesca Baracca, Alice Nadia Rossi, Bianca Maria Piraccini, Vittorio De Pietro, Valentino Marino Picciola, Alessandra Gelmetti, Iria Neri
https://doi.org/10.5826/dpc.1402a140

“Pilomatricoma is a tumor that arises more frequently in the pediatric population. In most cases, clinical presentation and dermoscopy are sufficient to diagnose or suspect it.”

OPINION
There Exist Educational Deficiencies in Specialized Dermatologic Care: Implications for Patients of Different Sexes, Genders, and Sexual Orientations
Isabella Mark, Michael Diaz, Jasmine Tran, Shari Lipner

---

REVIEW
Identifying SCC Lesions Capable of Spontaneous Regression by Using Immunohistochemistry: A Systematic Review and Meta-Analysis Study
https://doi.org/10.5826/dpc.1402a47

“The results of our study show that a number of biomarkers, including CD10, COX-2, and elastic fibers, have a high capability of differentiating between SCC lesions and lesions with the capability of spontaneous regression, such as KA, in cases with a difficult diagnosis.”

Photodynamic Therapy for the Treatment of Basal Cell Carcinoma: A Comprehensive Review of Randomized Controlled Trials
Ioannis-Alexios Kouprentziotis, Natalia Rompoti, Konstantinos Liopyris, Electra Nicolaidou, Alexander Stratigos
https://doi.org/10.5826/dpc.1402a105

“Many different randomized controlled trials have compared photodynamic therapy with other treatment modalities and have demonstrated that photodynamic therapy is a safe and efficacious option for the treatment of superficial basal cell carcinoma and to a lesser extent nodular basal cell carcinoma.”

Oral Diseases During Systemic Psoriatic Drugs: A Review of the Literature and Case Series
Annunziata Raimondo, Federica Di Spirito, Serena Lembo
https://doi.org/10.5826/dpc.1402a107

“This narrative review discusses on studies that describe oral adverse drug reactions in the context of systemic therapy for psoriasis.”

Efficacy of Intralosional Methotrexate Injection versus Triamcinolone Acetonide in Nail Psoriasis: A Systematic Review and Meta-Analysis
Stephanie Nathania, Diah Adriani Malih, Muslimin, Haridjan
https://doi.org/10.5826/dpc.1402a109

“ Intralosional injection therapy in nail psoriasis is a promising option. Both methotrexate and triamcinolone acetonide can be used and yield favorable outcomes.”

Tape Stripping — Searching for Minimally Invasive Biomarkers in Atopic Dermatitis
Weronika Zyskh, Magdalena Trzeciak
https://doi.org/10.5826/dpc.1402a123

“Stratum corneum samples collected by tape stripping provide a wide range of immune and epidermal barrier biomarkers. Although numerous potential biomarkers have been identified, none of these candidates have been validated and implemented into routine clinical practice yet.”

A Systematic Review of Diagnoses With Rosettes Under Dermoscopy
May Alorainy, Kendall Buchanan, Tyler Nussinow, Judy B. Robinowitz, Peggy Cyr, Elizabeth V. Seiverling
https://doi.org/10.5826/dpc.1402a125

“Rosettes are a dermoscopic finding seen in keratinocytic neoplasms. This systematic review shows that they are also observed in many other conditions. Comprehensive clinical evaluation is crucial for accurate diagnosis.”

Pilomatricoma: Clinical, Dermoscopic Findings and Management in 55 Pediatric Patients and Concise Review of the Literature With Special Emphasis on Dermoscopy
Marco Adriano Chessa, Maria Francesca Baracca, Alice Nadia Rossi, Bianca Maria Piraccini, Vittorio De Pietro, Valentino Marino Picciola, Alessandra Gelmetti, Iria Neri
https://doi.org/10.5826/dpc.1402a140

“Pilomatricoma is a tumor that arises more frequently in the pediatric population. In most cases, clinical presentation and dermoscopy are sufficient to diagnose or suspect it.”

OPINION
There Exist Educational Deficiencies in Specialized Dermatologic Care: Implications for Patients of Different Sexes, Genders, and Sexual Orientations
Isabella Mark, Michael Diaz, Jasmine Tran, Shari Lipner
RESEARCH LETTER

Disparities in Financial Burden, Outcomes, and Comorbidities Among Pediatric Patients With Pyoderma Gangrenosum With and Without Mental Health Disorders in a Multivariate Analysis of the 2016 Kids’ Inpatient Database
Amar D. Desai, Angela Lu, Faraz Yousefian, Shari Lipner
https://doi.org/10.5826/dpc.1402a57

Acral Arteriovenous Hemangioma: A Case Report and the Utility of Ultra-High Frequency Ultrasound (UHFUS) in Diagnosis
Stefania Guida, Antonio Podo Brunetti, Gianmarco Diego Bigotto, Giorgio Stabile, Franco Rongioletti
https://doi.org/10.5826/dpc.1402a89

Dermoscopic Evaluation of Combined Treatment With Fractional Co2 and Nanosecond Q-1064 nm Laser for Traumatic Facial Tattoo
Claudio Conforti, Piergiorgio Turco, Sebastian Lasagna, Domenico Piccolo, Vito Cazzato
https://doi.org/10.5826/dpc.1402a87

Dermoscopic Presentation of Two Cases of Pigmented Purpuric Dermatosis-like Mycosis Fungoides
Neil Vaishampayan, Andrew Schuler, Anne Ning, Alexandra Hristov, Douglas Fuller, Tito Kraj Tejasvi
https://doi.org/10.5826/dpc.1402a84

Parental Preferences Regarding the Novel Systemic Treatment for Atopic Dermatitis in Children
Alicja Mesjasz, Monika Łobaza, Marta Jaskulak, Magdalena Trzeciak
https://doi.org/10.5826/dpc.1402a108

Unusual Cause of Scalp Nodule in a Toddler
Smriti Gupta, Dipankar De, Sanjeev Handa, Debajyoti Chatterjee, Rahul Mahajan
https://doi.org/10.5826/dpc.1402a110

Could Conventional, Ultraviolet-Induced Fluorescence and Sub-Ultraviolet Reflectance Dermatoscopy Assist the Diagnosis of Cutaneous Collagenous Vasculopathy? A Case Report
Paweł Pietkiewicz, Adarsha Adhikari, Katarzyna Kowalska, Agnieszka Maślińska, Monika Bowszyc-Dmochowska
https://doi.org/10.5826/dpc.1402a77

Innovations in Dermoscopy Training: A Comparative Analysis of Dermoscopy Training Educational Delivery Models for Resident Physicians
T. Austin Black, Emelie Nelson, Anthony Teixeira, Travis Anthony, Julie Simon, Kelly Nelson
https://doi.org/10.5826/dpc.1402a122

Prominent Skin Markings in the Dermoscopic Evaluation of Melanocytic Lesions: The Importance of the Context
Laura Mateu-Arrom, Cristina López-Sánchez, Oriol Yélamos
https://doi.org/10.5826/dpc.1402a126

Granulomatous Dermatitis Characterized by the Manifestation of Tumor and Plaque Lesions Subsequent to Herpes Zoster: A Case Series
Dilekt Bayramgürler, Abdullah Demirbaş, Murat Durdu, Göktuğ Aslançoğlu, Tuğrul Eruyar, Güzey Demirkesen
https://doi.org/10.5826/dpc.1402a129

Hereditary Angioedema Exacerbated by Estrogen Supplementation Treatment for Uterine Fibroid — A Therapeutic Challenge
Alicja Mesjasz, Kinga Bojahr, Jan Romantowski, Marek Niedoszytko
https://doi.org/10.5826/dpc.1402a130

The ’Watch Sign’ – Another Observation in the Course of Male Frontal Fibrosing Alopecia
Jakub Żółkiewicz, Urszula Maślińska, Roman J. Nowicki, Michał Sobjanek, Martyna Stolarska
https://doi.org/10.5826/dpc.1402a132

Retrospective Cohort Study of Hepatic and Hematologic Toxicity in Terbinafine-Treated Onychomycosis Patients With Reduced Kidney Function at an Academic Institution
Kaya L. Curtis, Jose W. Ricardo, Yuqing Qiu, Debra K. Lee, Jamie Hedrick, Henry I. Lipner, Shari R. Lipner
https://doi.org/10.5826/dpc.1402a137

Circumscribed Acral Hypokeratosis: Clinical and Dermoscopic Signs of an Evolving Condition
Alessandra Petruzzellis, Eleonora Di Matteo, Luca Bianchi, Francesca Lupi, Ornella De Pita, Giuseppe Cianchini
https://doi.org/10.5826/dpc.1402a139

Dermoscopy of Thick Scalp Melanoma: Is It Always an Easy Diagnosis?
Sebastiano Pellerone, Chiara Pensa, Giustino Riccio, Gabriella Brancaccio, Giuseppa Argenziano, Elvira Moscarella
https://doi.org/10.5826/dpc.1402a143

IMAGE LETTER

Porokeratosis Ptychotropica Mimicking Anogenital Warts
Tugba Keuser Ustunbas Uzuncakmak, Necmettin Akdeniz, Pembe Gül Güneş
https://doi.org/10.5826/dpc.1402a111

Could Conventional, Ultraviolet-Induced Fluorescence and Sub-Ultraviolet Reflectance Dermatoscopy Assist the Diagnosis of Cutaneous Collagenous Vasculopathy? A Case Report
Paweł Pietkiewicz, Adarsha Adhikari, Katarzyna Kowalska, Agnieszka Maślińska, Monika Bowszyc-Dmochowska
https://doi.org/10.5826/dpc.1402a122

Prominent Skin Markings in the Dermoscopic Evaluation of Melanocytic Lesions: The Importance of the Context
Laura Mateu-Arrom, Cristina López-Sánchez, Oriol Yélamos
https://doi.org/10.5826/dpc.1402a126

Granulomatous Dermatitis Characterized by the Manifestation of Tumor and Plaque Lesions Subsequent to Herpes Zoster: A Case Series
Dilekt Bayramgürler, Abdullah Demirbaş, Murat Durdu, Göktuğ Aslançoğlu, Tuğrul Eruyar, Güzey Demirkesen
https://doi.org/10.5826/dpc.1402a129

Hereditary Angioedema Exacerbated by Estrogen Supplementation Treatment for Uterine Fibroid — A Therapeutic Challenge
Alicja Mesjasz, Kinga Bojahr, Jan Romantowski, Marek Niedoszytko
https://doi.org/10.5826/dpc.1402a130

The ‘Watch Sign’ – Another Observation in the Course of Male Frontal Fibrosing Alopecia
Jakub Żółkiewicz, Urszula Maślińska, Roman J. Nowicki, Michał Sobjanek, Martyna Stolarska
https://doi.org/10.5826/dpc.1402a132

Retrospective Cohort Study of Hepatic and Hematologic Toxicity in Terbinafine-Treated Onychomycosis Patients With Reduced Kidney Function at an Academic Institution
Kaya L. Curtis, Jose W. Ricardo, Yuqing Qiu, Debra K. Lee, Jamie Hedrick, Henry I. Lipner, Shari R. Lipner
https://doi.org/10.5826/dpc.1402a137

Circumscribed Acral Hypokeratosis: Clinical and Dermoscopic Signs of an Evolving Condition
Alessandra Petruzzellis, Eleonora Di Matteo, Luca Bianchi, Francesca Lupi, Ornella De Pita, Giuseppe Cianchini
https://doi.org/10.5826/dpc.1402a139

Dermoscopy of Thick Scalp Melanoma: Is It Always an Easy Diagnosis?
Sebastiano Pellerone, Chiara Pensa, Giustino Riccio, Gabriella Brancaccio, Giuseppa Argenziano, Elvira Moscarella
https://doi.org/10.5826/dpc.1402a143

IMAGE LETTER

Porokeratosis Ptychotropica Mimicking Anogenital Warts
Tugba Keuser Ustunbas Uzuncakmak, Necmettin Akdeniz, Pembe Gül Güneş
https://doi.org/10.5826/dpc.1402a111

Human Cutaneous Dirofilariasis Caused by Dirofilaria repens
Victoria Mattutuz, Céline Nourrisson, Clément Theis, Carole Chevenet, Philippe Poirier, Maxime Moniot
https://doi.org/10.5826/dpc.1402a102

A Lesion Surrounded by the Rainbow: Merkel Cell Carcinoma
Melek Aslan Kayıran, Ahmet Sait Sahin, Bengu Cobanoglu Simseh
https://doi.org/10.5826/dpc.1402a64

Cutaneous Metastases as a First Sign of Gastric Adenocarcinoma
Marta Prtajin, Daniela Ledić Drvar, Daška Štulhofer Buzina, Ružica Jurakić Tončić, Ivana Ilić, Romana Čeović
https://doi.org/10.5826/dpc.1402a67

Steatocystoma Simplex of the Vulva
Anna Mishina, Vergil Petrovici, Ecaterina Foca, Igor Mishin
https://doi.org/10.5826/dpc.1402a72

Bullous Kaposi Sarcoma: An Uncommon Blistering Variant in an HIV-Negative Patient
Eleonora Gherardi, Luca Tinunin, Tommaso Grassi, Vincenza Maia, Veri Grandi
https://doi.org/10.5826/dpc.1402a113
Glibenclamide - Induced Photoallergic Reaction
Eva Rupert Gostiša, Ružica Jurakić Tončić, Stefano Caccavale, Romana Čeović
https://doi.org/10.5826/dpc.1402a114

Dermoscopic Findings in Mycobacterium Immunogenenum Skin Infection
Pablo Vargas Mora, José Magna Aguirre, Paula Almeida Abarcia
https://doi.org/10.5826/dpc.1402a115

A Nodular Melanoma Mimicking a Blue Nevus a Case Report
Giovanni Marco D’Agostino, Tommaso Bianchelli, Giulia Veronesi, Valentina Di Gregorio, Donatella Brancorsini
https://doi.org/10.5826/dpc.1402a116

Chagas Disease (American Trypanosomiasis)
Stefano Veraldi, Gianluca Nazzaro
https://doi.org/10.5826/dpc.1402a81

Nilotinib Induced Keratosis Pilaris in a Female With Chronic Myeloid Leukemia
Ranjana Beniwal, Akriti Agrawal
https://doi.org/10.5826/dpc.1402a82

Vulvar Acantholytic Warty Dyskeratoma
Sabina Vaccari, Luca Rapperini, Cosimo Mischiai, Emi Dika
https://doi.org/10.5826/dpc.1402a124

Pigmented Eccrine Poroma on the Palm Mimicking Nodular Melanoma
Inghilde Damanielle Silva, João Paulo Monteiro Yamagata, Thales Pereira de Azevedo, Maria Auxiliadora Jeunon Sousa, Thiago Jeunon de Sousa Vargas
https://doi.org/10.5826/dpc.1402a131

Trichomycosis Axillaris: An Underdiagnosed Hair Shaft Condition
Juan Manuel Liñán-Barroso, Norberto Sánchez-Rodríguez
https://doi.org/10.5826/dpc.1402a134

Pigmented Eccrine Poroma on the Palm Mimicking Nodular Melanoma
Inghilde Damanielle Silva, João Paulo Monteiro Yamagata, Thales Pereira de Azevedo, Maria Auxiliadora Jeunon Sousa, Thiago Jeunon de Sousa Vargas
https://doi.org/10.5826/dpc.1402a131

Trichomycosis Axillaris: An Underdiagnosed Hair Shaft Condition
Juan Manuel Liñán-Barroso, Norberto Sánchez-Rodríguez
https://doi.org/10.5826/dpc.1402a134
The so-called “gray zone”, where the distinction between nevi and melanoma becomes blurred, continues to be the source of heated debates. Whether we like it or not, the “gray zone” is a reality due to the inherent complexity of melanoma biology and the limitations of our diagnostic methods. However, the concept of a “gray zone” can also be seen as fictional, as it leads to contradictory conjectures about the biological outcome of a specific melanocytic lesion. A lesion cannot be both benign and malignant simultaneously; one of these two assertions must be wrong. In practice, uncertain diagnoses present a challenge, as both doctors and patients seek definitive diagnoses and want solid treatment decisions. This quest for certainty is undermined by ambiguous terms such as “dysplastic nevus”, “melanocytic tumor with uncertain malignant potential” or, more recently, “melanocytoma”. These terms have the characteristic of eluding a precise definition and becoming loaded with all kinds of meaning, often leading to confusion. It is also unclear if these terms reflect biologic uncertainty (“the lesion does not know what it is”) or diagnostic uncertainty (“the pathologist does not know what it is”).

The idea of an intermediate biological state between nevus and melanoma is rooted in the broader concept of step-wise tumor progression, which in turn is based on the theory of evolution. It suggests a gradual transformation from benign to malignant states, reflecting a process of malignant transformation by accumulating oncogenic mutations and adaptation to the environment by selection. Early studies on melanoma, such as those by Ackerman in the late 1940s, introduced the idea that melanoma originates from preexisting nevi [1]. This was further supported by Allen and Spitz in 1953, who posited that all melanomas begin in a preexisting mole, particularly in an “active junctional nevus” [2]. These foundational beliefs have influenced melanoma diagnosis and management for decades. The introduction of the “dysplastic nevus” concept in the mid-1970s added complexity to this narrative. “Dysplastic nevus”, characterized by architectural disorder and cytologic atypia, were proposed as intermediates in the transformation from nevi to melanoma [3]. From the start, this concept has been a source of debate, primarily due to the challenges in reproducibly identifying “dysplastic” features and assessing their true risk of progression to melanoma.

To enhance its utility in clinical practice and provide a clear target for intervention, the concept of the biological “gray zone” underscores the importance of identifying a specific lesion that embodies this gray zone. The “dysplastic nevus” offers a tangible example of this concept. However, the
stepwise tumor progression model, although supported by extensive research within and beyond melanocytic biology, does not always align with a clinically visible “intermediate” or “precursor” lesion. Sometimes, a clear precursor or intermediate lesion is absent, as for example in basal cell carcinoma (BCC). The lack of ambiguity in diagnosing BCC could be attributed to its distinct microscopic appearance, which facilitates straightforward identification, bypassing the need for the identification of intermediate, ambiguous stages. In the case of BCC, the absence of a diagnostic gray zone prevents speculation about a biological gray zone. This stands in stark contrast to the ambiguity encountered in diagnosing melanocytic proliferations.

The World Health Organization’s (WHO) latest classification of melanocytic tumors acknowledges the complexity of classifying melanocytic proliferations into purely benign or malignant categories [4]. The new classification incorporates traditional histogenetic patterns, molecular alterations, and UV exposure within a pathway model that delineates nine distinct pathways. Each pathway traces the progression from benign precursor lesions to intermediate stages and, ultimately, to melanoma. The WHO classification concedes that, for some pathways, clear precursor or intermediate lesions remain unidentified, leaving open the possibility that such stages might not exist and could be fictional rather than real. The updated WHO classification also attempts to better define the concept of the intermediate lesion, introducing the term “melanocytoma” for this purpose. Examples include BAP1-inactivated melanocytoma, pigmented epithelioid melanocytoma, and Spitz melanocytoma. According to the WHO classification, these tumors are characterized by harboring more than one oncogenic mutation. Whether these tumors truly represent intermediate lesions, as suggested by the pathway concept, or are akin to the “dysplastic nevus”—essentially nevi with specific morphological features and a more complex array of somatic mutations that generally do not progress to melanoma—remains a matter of debate. My inclination is to support the latter interpretation.

Although there is the hope that molecular techniques will eliminate diagnostic grey zones, it is important to recognize that edge cases will persist. They may become less frequent but will not vanish entirely. Techniques like immunohistochemistry, in situ hybridization, and comparative genomic hybridization may offer crucial insights for “borderline” lesions. Yet, as most dermatopathologists know, usually these tools do not fully solve ambiguous cases. Even with cutting-edge methods like whole-genome sequencing, eradicating gray zones may remain unattainable. The unpredictable nature and individual variability of biological systems ensure that some level of uncertainty persists. Diagnoses are, in essence, conjectures. Biological processes, though seemingly deterministic, are influenced by chaotic elements. This concept, echoing chaos theory, suggests that minor differences in initial conditions—spanning from the specific set of somatic mutations to the microenvironment and the individual immune status—can significantly impact outcomes. In this sense, biology shares similarities with meteorology: making a diagnosis is more akin to forecasting the weather than to reading a clock.

In the context of medical diagnostics and treatment, the advent of Artificial Intelligence (AI), especially multimodal AI, holds the promise of significantly reducing the various diagnostic and biologic gray zones discussed so far. Multimodal AI, by integrating data from diverse sources such as imaging, genetic information, and electronic health records could offer a more nuanced and comprehensive understanding of cancer biology [5]. This integration could lead to more accurate diagnoses of melanocytic proliferations and vanishing gray zones. However, it is crucial to recognize that AI, regardless of its sophistication, cannot eliminate all forms of uncertainty. Even with technological advancements, the individual preferences of dermatologists and patients regarding the trade-off between sensitivity and specificity will continue to exist [6]. These preferences shape decision-making and treatment approaches, underscoring the importance of personalized care.

Ambiguity in diagnosis of melanocytic proliferations is an inescapable reality. Some of this ambiguity is a product of human interpretation, while the rest is deeply embedded in the complex biology of melanocytic tumors. Grey zones can be a source of anxiety, lead to delayed treatment, and, at times, result in unnecessary procedures. Therefore, navigating these uncertain waters with as much precision and clarity as possible is crucial. For us clinicians it is important to distinguishing between different types of gray zones. We should be aware that pathology reports may obscure diagnostic uncertainty with language that implies biological uncertainty instead. Recognizing these distinctions is vital for healthcare professionals in managing and communicating about “borderline” lesions. Finally, there is a silver lining: “Gray zones” also open up opportunities; they challenge us to refine our diagnostic methods and question our concepts and definitions. Furthermore, their existence reminds us as researchers that science never ends and forces us as clinicians to develop appropriate strategies in the face of uncertainty.
References

Biologic Gray Zone of Melanocytic Tumors in Reality: Defining ‘Non-Conventional’ Melanocytic Tumors

Gerardo Ferrara¹, Alberto Gualandi¹, Nathalie Rizzo²

1 Istituto Nazionale Tumori IRCCS Fondazione ‘G. Pascale’, Naples, Italy
2 IRCCS Ospedale San Raffaele, Milan, Italy

The ‘gray zone’ and the ‘borderline malignant’ concepts are widely used in Surgical Pathology because of their considerable explanatory potential; however, they require a rigorous definition, since, as their very name suggests, they move within an ambiguous terrain (between white and black; ‘borderline’ between benign and malignant; and, specifically, ‘borderline’ between nevus and melanoma). Confusion exists between intermediate (borderline) morphology and intermediate (borderline) biology, both ‘intermediates’ being often approached with the same set of histopathological criteria, which, in our opinion, is a conceptual and practical mistake.

The concept of morphologically intermediate melanocytic neoplasms is implicit to the assumption that melanomas and nevi are “reciprocal morphological simulators”; the differential diagnosis between couples of simulators is based upon the simultaneous evaluation of a standard set of criteria which are subjectively implemented and evaluated, thereby bearing an inherent diagnostic uncertainty (and, parenthetically, a poor interobserver agreement) in some cases [1].

The concept of biologically intermediate melanocytic tumors is referred to neoplasms which are sticto sensu neither nevi or melanomas and are therefore not evaluable as couples of simulators. These tumors are identified as melanocytomas by the World Health Organization (WHO) [2]; we also define melanocytomas as “non-conventional melanocytic tumors”, in order to underline their peculiar clinicopathological and biological properties [3].

The melanocytoma rubric encompasses:

i. tumors with a lymphotropic pattern of spread: pigmented epithelioid melanocytomas (PEM); atypical Spitz tumors (AST); WNT-activated/plexiform/deep penetrating tumors (DPN);

ii. other dermal-based tumorigenic neoplasms which, in spite of their histopathological atypia, are seldom associated with distant metastasis: BAP1 inactivated melanocytic tumors (BIMT); MITF pathway-activated (PEComa-like; clear cell sarcoma-like) melanocytic tumors (MAMT);

iii. in our opinion, also cellular blue nevus (CBN)-related dermal dendritic melanocytic neoplasms [4].

There is little doubt that many melanocytomas are so atypical that in a dichotomous (nevus vs melanoma) diagnostic approach they should be labelled as ‘melanoma’, and mostly as ‘thick melanoma’. Nevertheless, all of them are associated with a very low incidence of distant metastases even...
after spread to the regional nodes, the latter being found in a percentage (e.g.: up to 39% in AST [5]) even higher than in melanoma. The nodal melanocytoma deposits have a metastatic (subcapsular/intraparenchymal) morphological pattern (Figure 1), different from the capsular/settal pattern of nodal nevi. An abnormal spread to the nodes, if there were any, from common/dysplastic nevi should be a trivial incidental finding, given the frequency of common nevi and the high number of nodes which are daily examined from surgical specimens. We can thus conclude that some melanocytomas are ‘lymphotropic neoplasms’, whereas common/dysplastic nevi are not.

For the above, the nevus vs melanoma diagnostic approach might be retained only by labelling melanocytomas as ‘low-grade melanoma’; the latter term, however, is incorrect because the genetic profile of these neoplasms is different from melanoma. Indeed, based on the presence of specific driver mutations, The Cancer Genome Atlas (TCGA) identifies four molecular melanoma subtypes: B\(\text{RAF}\)-mutated, R\(\text{AS}\)-mutated, N\(\text{F1}\)-mutated, and triple wild-type (a heterogeneous group characterized by one of the following: K\(\text{IT}\) mutations; early onset of K\(\text{IT}\), C\(\text{CNND1}\), C\(\text{DK4}\), M\(\text{ITF}\), and T\(\text{ERT}\) amplification; gene deletion/loss-of-function of TP\(\text{53}\) and CD\(\text{KN2A}\)) [6]. With the exception of B\(\text{RAF}\) mutation of ‘combined’ (nevus-associated) subtypes, the genetic drivers of melanocytomas are completely different [2]:

- in PEM: P\(\text{RKAR1A}\) inactivation (in ‘combined’ tumors) or P\(\text{RKCA}\) fusion;
- in AST: H\(\text{RAS}\) activating mutations; activating fusions of receptor tyrosine kinases ROS\(\text{I}\), ALK, N\(\text{TRK}\)\(\text{I/2/3}\), MET, M\(\text{ERTK}\), RET; activating fusions of MAP kinases B\(\text{RAF}\), R\(\text{AF1}\), MAP\(\text{3K8}\);

![Figure 1](image_url)

**Figure 1.** A-D) A ‘Spitz-like’ tumor of the thigh in a 7-year-old boy. The tumor is wedge-shaped but asymmetric (A) and with confluent (non-random) pleomorphism of epitheliod cells (B); there is a deep dermal desmoplasia. The sentinel node was positive with multiple small subcapsular aggregates of S\(\text{100}\)-positive cells (D). The patient is alive with no evidence of disease 17 years after surgery. Retrospective molecular examination has revealed H\(\text{RAS}\) G13R (p.Gly13Arg) mutation, which is typical of a subset of Spitz tumors morphologically typified by deep desmoplasia. E-H) A PEM removed from the ear in a 36-year-old woman. The tumor is heavily pigmented throughout (E), with epidermal hyperplasia and obliteration of the grenz zone (F); in less pigmented areas the nuclei show a typical ‘fried egg’ appearance (G); isolated HMB45-positive intraparenchymal tumor cells were found in the sentinel node (H; Courtesy of Dr. Antonio Perasole, Vicenza, I). No follow up data are available.
• in DPN: gain-of-function mutations in CTNNB1 or, less commonly, loss-of-function mutations in APC;
• in BIMT: loss-of-function mutation in BAP1;
• in MAMT: ACTIN::MITF or MITF::CREM fusions.
• In CBN: activating mutations in GNAQ, GNA11, or PLCB4 (or less frequently, in CYSLTR2).

Unfortunately, the full spectrum of initiating mutations in melanocytomas, remains to be characterized; in addition, a melanocytoma-like morphology may be associated with immunohistochemical and/or genetic findings of ‘conventional’ melanoma (Figure 2). Thus, a new problem is raising in dermatopathology, i.e.: the differential diagnosis between severely atypical melanocytoma and melanocytoma-like ‘conventional’ melanoma [3]. A flow-chart addressing this problem for neoplasms with ‘Spitz-like’ morphology is shown in Figure 3.

Upon recognition of a melanocytoma, it is suggested that low-grade and high-grade tumors must be differentiated on the basis of a list of general criteria, shared among the various melanocytoma subgroups [7]. In our routine histologic reports we do lists the atypical features of any melanocytoma, but with the following caveats:

1. A persistent conceptual contamination is evident between the melanocytoma grading and the risk of progression from melanocytoma to melanoma [2,7]; however, such a progression is even more exceptional than the nevus-melanoma progression [8];

2. A list of general criteria alone cannot work, since each melanocytoma subgroup has its own classical features and, therefore, its atypical features (e.g.: a ‘brisk’ lymphocytic infiltrate is typical for BIMT but atypical for other melanocytomas) [3,4];

3. Modulating the clinical management of melanocytomas on the basis of their histologic grade is inaccurate, because the relationship between morphological atypia and biological risk has been unproven (actually denied in the seminal paper on PEM [9]).

From a conceptual point, the definition of melanocytoma is not compatible with the terms ‘nevus’ and ‘melanoma’; for practical purposes, however, we use the term ‘nevus’ for melanocytomas whose atypical features (as listed in [4]) are inconsistent. For all melanocytomas with atypical features, we recommend a narrow re-excision followed by periodic ultrasonographic monitoring of the regional nodes. Management as per melanoma of the same thickness should be recommended only for melanocytic tumors of uncertain malignant potential (MELTUMP), defined as severely atypical tumorigenic melanocytic neoplasms in which: i) morphology is in between a melanocytoma and a melanocytoma-like melanoma; and ii) a specific genetic driver is not identified [10]. Of course, each case should be evaluated in a multi-disciplinary context by also considering the clinical data, namely: the patient’s age; the location and the clinical features of the tumor.

**Figure 2.** A-C) A melanocytic tumor removed from the cheek in a 19-year-old man. The tumor has a nodular silhouette with superficial melanin deposition (A); the epidermis is flattened but uninvolved (B); the dermal tumor shows spindle and epithelioid cells with confluent growth and confluent pleomorphism. In spite of the ‘Spitz-like’ cytological features, molecular examination revealed KIT p.Val569_Asp572del mutation and was thus diagnosed as melanoma.
In conclusion, the biological gray zone of melanocytic tumors is currently identified in melanocytomas, whose peculiar genetic, histological, and biological features request a peculiar (‘non-conventional’) clinicopathological approach.

References

Considerations on The Biologic Gray Zone of Melanocytic Tumors

Giorgio Annessi¹, Emanuele Annessi¹

¹ Dermatopathology Unit, Istituto Dermopatico dell’Immacolata, IRCCS, Roma, Italy

Dermatologists are well aware that there exist some melanocytic lesions which are morphologically very difficult to classify as benign or malignant and consequently of uncertain biological potential. This may be due partly on the biological complexity of such lesions and partly on the limitations of our diagnostic methods. We believe the introduction of new entities in the field of melanocytic lesions should be always accompanied with the formulation of specific, reliable and reproducible clinicopathologic criteria. Furthermore, a new entity makes sense when its recognition is of real practical use for patient management and care. In particular, the aim of the pathologist, despite the complexity of the subject, should be to render diagnoses that are as simple as possible, easy for clinicians to understand and above all that guide an appropriate therapeutic approach.

Actually, the World Health Organization (WHO) attempt to provide a new classification of melanocytic lesions on the basis of a model of tumor progression seems a bit forced to us (1). In fact, instead of proceeding from histological experience to create a model, WHO started from the theoretical model of tumor progression and within this, they tried to adapt the observations derived from histological experience. This unusual way of proceeding has led to the creation of a series of hypothetical “intermediate” entities, grouped under the term melanocytomas/MELTUMP (BAP-1 inactivated melanocytoma, Deep penetrating melanocytoma, PEM, Atypical Spitz Tumor, STUMP and Atypical cellular blue nevus/melanocytoma) that together would constitute the so-called grey-zone of melanocytic lesions (1-5). In addition, within each of these entities it would be possible to recognize further subtypes on the basis of atypia grading (6). However, although WHO has established apparently specific clinical, histological and genetic criteria for identifying each of these entities, their applicability in daily clinicopathological practice has proven to be very difficult. In fact, both the clinical and especially the histological criteria are far from being specific and reliable; in particular, interobserver reproducibility among pathologists, even the most experienced ones, has turned out to be poor with diagnostic arbitrariness reigning supreme. Overall, this results in a terrible confusion of terminology that disorients clinicians and an absolute lack of consensus regarding the treatment of these lesions. To demonstrate this confusion, some authors recommend treating melanocytomas with re-excision followed by periodic ultrasonographic monitoring of the regional nodes and those with major atypical features (MELTUMP) with “…management as per melanoma of the same thickness”. (7) In practice, they propose the same treatment for melanocytomas/
Furthermore, the use of the single term (LgM) would relieve the pathologist of the difficult, at times impossible, task of recognizing a series of confusing, poorly reproducible and purely theoretical histological entities. Again, the term LgM clearly informs clinicians about both the nature of the lesion and the biological behaviour to be expected (low metastatic risk). Finally, it indicates to clinicians the appropriate treatment and management of the patient.

While waiting for new methods to allow more precise and perhaps personalized diagnoses, at the moment the one proposed seems to me the “less imperfect” solution to the problem of the gray-zone of melanocytic lesions.

References


The Gray Zone of Melanocytic Tumors - A Clinical Point of View

Camila Scharf¹, Giulia Briatico¹, Gabriella Brancaccio¹, Elvira Moscarella¹, Andrea Ronchi², Giuseppe Argenziano¹

¹ Dermatology Unit, University of Campania L. Vanvitelli, Naples, Italy
² Pathology Unit, University of Campania L. Vanvitelli, Naples, Italy

As discussed by Kittler and Ferrara, melanocytic lesions, particularly those exhibiting challenging histopathologic features, pose a significant diagnostic and therapeutic dilemma for clinicians. While Kittler navigates the nuanced territory of diagnosing melanocytic proliferations, critically examining the notion of the gray zone, debating its reality versus its conceptual fiction, the author also assumes that a melanocytic lesion cannot simultaneously be benign and malignant, highlighting the dichotomy between biological and diagnostic uncertainties.

The World Health Organization’s latest classification of melanocytic tumors attempts to navigate these complexities by delineating distinct pathways of progression from benign to malignant lesions. [1] Yet, the classification acknowledges the persistent ambiguity in defining clear precursor lesions for some pathways, highlighting the ongoing debate between biological versus diagnostic gray zones, as implicated by Ferrara.

From the 1970’s, when first described, dysplastic nevus (DN) has always been a source of confusion. The key is whether, and to what level, DN represents a premalignant lesion that will progress to melanoma. [2] This assumption has been propagated over the years, considering that grading nevus cytologic atypia as mild, moderate, or severe by the pathologists could imply this continuous progression of DN towards melanoma, as it happens in actinic keratosis. [3]

It is true that numerous studies have documented the relationship between DN and familial melanoma, and in fact, they were originally described in melanoma-prone families, with the implication that such lesions had a higher risk of transformation to melanoma than the patients’ regular nevi. However, in patients with familial melanoma and those with a high number of DN, still melanoma is most frequently developing de novo and not in association to a pre-existing DN. [4]

The basic concept included in the last WHO classification is that all melanomas develop from a benign precursor. The latter progresses first to a biologically intermediate lesion (DN, melanocytoma, atypical Spitz tumor, etc.) that finally transforms into a melanoma. The point is that clinically this concept if very difficult to believe, mainly for the following evidence:

1. More than 70% of melanomas are not found histopathologically in association to a pre-existing nevus.
2. How can it be possible that no nevus remnants are
found in such a high number of melanomas if it were true that all of them should be the result of a nevus transformation?

2. Of the minority of melanomas (less than 30%) found in association to a pre-existing nevus, more than half are associated to a common dermal nevus and not to a DN. [6] How can it be possible that the biologically intermediate lesion is so frequently missing if the stepwise transformation were true?

3. The probability of a single nevus to transform into melanoma is exceedingly low, being calculated in the order of 1 out 200.000 nevi and even in patients with multiple nevi still melanoma develops most frequently de novo. [7]

Although we believe the presence of multiple nevi in an individual is associated with increased melanoma risk, nevi are not melanoma precursors, and DN, melanocytomas and atypical Spitz tumors are not nevi evolving into melanoma but benign lesions with challenging histopathological features.

References

Correlation Among Serum Calcidiol, Sun Index, and Vitamin D Intake in Individuals With Seborrheic Keratoses Living in Coastal Area

Izzah Aulia¹, Larisa Paramitha Wibawa¹, Lis Surachmiati Suseno¹, Nurul Ratna Mutu Manikam²

¹ Dermatology and Venereology Department, Faculty of Medicine, Universitas Indonesia – dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia
² Department of Nutrition, Faculty of Medicine, Universitas Indonesia – dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia

Key words: calcidiol, seborrheic keratosis, sun, vitamin D

Citation: Aulia I, Wibawa LP, Suseno LS, Manikam NRM. Correlation Among Serum Calcidiol, Sun Index, and Vitamin D Intake in Individuals With Seborrheic Keratoses Living in Coastal Area. Dermatol Pract Concept. 2024;14(2):e2024037.

DOI: https://DOI.org/10.5826/dpc.1402a37

Accepted: November 1, 2023; Published: April 2024

Copyright: ©2024 Aulia et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Larisa Paramitha Wibawa, MD, Dermatology and Venereology Department, Faculty of Medicine, Universitas Indonesia – dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. Phone number: +62 821-1311-8480
E-mail: larisa.paramitha@ui.ac.id

ABSTRACT

Introduction: Seborrheic keratoses (SK) are benign epidermal tumors with high sun exposure as a major risk factor. Vitamin D deficiency is also thought to play a role in its pathogenesis. There has been no data regarding SK, calcidiol level, vitamin D intake, and sun index (SI) among people living in coastal areas in Indonesia.

Objectives: To assess the correlation between 1) serum calcidiol levels with SI and vitamin D intake and 2) lesion size with SI and serum calcidiol level among SK patients living in a coastal area.

Methods: This is a cross-sectional study. We performed interviews using the sun index questionnaire and semiquantitative food frequency questionnaire for vitamin D; physical examination; dermoscopy to determine the largest SK lesion size; and measurement of serum calcidiol levels in participants with SK living in Cilincing District, North Jakarta. Spearman correlation test was used to assess the relationship between variables.
Introduction

Seborrheic keratoses (SK) are benign epidermal tumors estimated to be present in 20% of adults, especially in the elderly [1,2]. Sun exposure was considered as the main risk factor for SK [1]. Genetics, mutations of specific genes, human papillomavirus infection, and vitamin D deficiency were also thought to play a role in the pathogenesis of SK [2,3]. Various studies pointed to the association between vitamin D deficiency and SK, especially gene mutation studies and the use of topical vitamin D analogs to treat SK lesions [4,5].

Vitamin D deficiency is fewer in Brazil and England populations living closer to the sea due to high sun exposure [6,7]. Indonesia is a tropical climate country with many coastal areas. Jakarta, as one of its cities, has a 12-hour duration of sun exposure with the highest average ultraviolet (UV) index of 10-12 [8]. Despite the exposure, vitamin D deficiency was common in various populations in Indonesia [9-11]. In addition to its endogenous synthesis with the aid of sun exposure, 10%-20% of vitamin D in the body is obtained from foods [12,13]. Low vitamin D intake is also a risk factor for vitamin D deficiency [11,14]. Indonesians have darker skin tones from light brown to dark brown (Fitzpatrick skin types 4 and 5).

Objectives

To our knowledge, data on serum calcidiol levels, sun index, and vitamin D intake among people with SK living in Indonesian coastal communities remains limited. Therefore, we aim to obtain baseline data regarding calcidiol level, sun exposure, and vitamin D intake among people with SK who live in coastal areas in Indonesia. Furthermore, we would explore the correlation between serum calcidiol levels with sun exposure and vitamin D intake among this population.

Methods

This cross-sectional study was conducted in the Cilincing district, North Jakarta, Indonesia on 10–12 November 2020. During the study, we implemented protocols for Coronavirus Disease 2019. We reported this study following the STROBE checklist for cross-sectional studies.

Subjects aged 18–59 years with SK lesions based on clinical examination and dermoscopy were enrolled consecutively in this study [15-17]. Impaired vitamin D absorption and metabolism were often found in geriatrics, so this age group was not included in this study [11]. Furthermore, through interview, we excluded subjects who took vitamin D supplements; received therapy for SK in the past month; had routine sunscreen use; had impaired renal or liver function; had a history of malabsorption diagnosis; were pregnant or breastfeeding during the recruitment period; or were grade II or morbid obesity according to the WHO Category for Asia-Pacific Region [18].

The primary outcome measure of this study was the correlation of serum calcidiol level with vitamin D intake and sun index. Furthermore, we would explore the correlation of the largest lesion size with calcidiol level and sun index. We recorded baseline characteristics such as age, sex, and occupation. We also collected basic anthropometric data, food intake, sun index, SK clinical characteristics, and serum calcidiol levels.

Anthropometric data was measured by using a digital scale and microtoise. Trained nutritionists assessed macronutrient intake with the 24-hour food recall and vitamin D intake with a semiquantitative food frequency questionnaire (FFQ) under supervision of clinical nutrition specialist (N.R.M.M.). One researcher (I.A.) did the interview to measure sun exposure with the sun index questionnaire. The sun index (SI) is an index for objective sun exposure measurement by multiplying the fraction of body surface area (BSA) by the duration of exposure on weekdays and weekends/holidays [19]. Another researcher who was blinded to the sun index and vitamin D assessment recorded the physical and dermoscopic examination by using a standard camera. Two board-certified dermatolovenereologists (L.P.W. and L.S.S.) oversaw the examination. We measured the SK largest diameter, specified its region, and categorized the lesions based on whether they were sun-exposed or partially exposed. The sun-exposed area was defined as the neck and V-neck area, outer forearms, or back of hands, whereas the

Results: Thirty-nine participants with SK aged 19–59 years were analyzed. The median of the SK largest diameter, SI, serum calcidiol, and vitamin D intake was 2 (1–10) mm, 3.95 (1.1–23.52), 14.3 (5.23–35.30) ng/ml, and 4.3 (0.1–30.1) mcg/day, respectively. SI and vitamin D intake were not significantly correlated with calcidiol levels. Similarly, SI and calcidiol levels were not significantly correlated with the largest SK lesion size.

Conclusions: We found low calcidiol levels and vitamin D intake in this coastal population. The SI and vitamin D intake had no correlations with calcidiol levels. Furthermore, calcidiol levels and SI had no correlations with the lesion largest diameter.
partially exposed area included the trunk, upper arms, flexor forearms, legs, and V-neck area. Serum calcidiol levels were measured by using LIAISON® analyzer (DiaSorin) and classified according to the Endocrine Society Classification [20].

**Ethics Statement**

This study was conducted following the Declaration of Helsinki and approved by the Health Research Ethics Committee Faculty of Medicine Universitas Indonesia (no. KET1003/UN2.F1/ETIK/PPM.00.02/2020). Written informed consent was obtained for all subjects before study enrollment.

**Statistical Analysis**

We calculated the minimum sample size to detect an $r$ of 0.45 with an $\alpha$ error rate of 5% and 80% power to be 36 subjects. All data were analyzed using SPSS® IBM® ver.20 (IBM Corporation). Subjects with missing outcome data were dropped out from the final analysis. Data distribution was determined using the normality test.

Pearson or Spearman correlation test was performed to assess the correlation of serum calcidiol with the sun index and vitamin D intake. Furthermore, we also assess the correlation of the largest lesion size with the serum calcidiol and sun index. The correlation value was defined using the $r$ correlation coefficient: 0.7–1.0 as a strong correlation, 0.3–0.69 as a moderate correlation, and 0–0.29 as a weak correlation. A P value less than 0.05 was considered statistically significant.

**Results**

Among 80 assessed for eligibility, 40 subjects were eligible and consecutively enrolled. The blood sample of one subject was lysed, so he was dropped out of the analysis. A total of 39 subjects were included in the final analysis (Figure 1). Most of the subjects were women. The median age was 40.5 (21–59) years. The median BMI was 25.7 (15.81–29.06) kg/m². More than half of the subjects were formal employees. The complete sociodemographic and clinical characteristics are described in Table 1.

Most patients (97.4%) had the largest lesion in the sun-exposed areas; only one subject had it on the trunk. There was a significant difference in the largest lesion diameter among age groups: 1 (1–3) mm at the 19–29 years, 2 (1–4) at the 30–39 years, 3 (1–10) mm at the 40–49 years, and 3 (1–7) mm at the 50–59 years group ($P = 0.016$). There was no significant difference in lesion diameter among subjects with low SI ($<4$) compared to high SI ($>4$) (2.00 [1–10] mm versus 2 [1–9] mm, $P = 0.815$). The mean size of lesions in the vitamin D deficient, insufficient, and normal groups was 2 (1–10) mm, 2 (1–9) mm, and 3 (1–5) mm, respectively ($P = 0.995$). The mean number of calcidiol levels were similar across all age groups, with the absolute values in the 19-29, 30–39, 40–49, and 50–59 years of age were 14.83 (6.82), 17.33 (9.43), 17.40 (10.03), and 14.08 (4.05) ng/ml, respectively ($P = 0.686$). Most of the subjects (71.8%) had vitamin D deficiency. However, vitamin D deficiency was more commonly found among the older age group than the younger age group (80% versus 63.2%, $P = 0.209$). The serum calcidiol had an increasing trend according to the sun exposure duration increment. In the group with sun exposure <14 hours/week, 14-28 hours/week, and >28 hours/week, the serum calcidiol level was 11.3 [10.2–18.7], 14.3 [7.25–26.20], and 15.1 [5.25–35.30] ng/ml, respectively ($P = 0.569$) (Figure 2). The value of SI in the vitamin D deficient was lower compared to the insufficient or normal group (3.82 [1.1 –17.64] versus 6.83 [2.21–23.52], $P = 0.177$) (Figure 3).
Table 1. Sociodemographic and clinical characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N (%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>Women</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td>Age (year), median (min-max)</td>
<td>40.5 (21–59)</td>
</tr>
<tr>
<td>19-29, N (%)</td>
<td>11 (28.2)</td>
</tr>
<tr>
<td>30-39, N (%)</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td>40-49, N (%)</td>
<td>8 (20.5)</td>
</tr>
<tr>
<td>50-59, n (%)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>BMI category, N (%)</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Normal</td>
<td>7 (17.9)</td>
</tr>
<tr>
<td>Overweight</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Grade 1 obesity</td>
<td>25 (61.5)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (min-max)</td>
<td>24.82 (3.59)</td>
</tr>
<tr>
<td>Occupation, N (%)</td>
<td></td>
</tr>
<tr>
<td>Fishermen</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Fishmongers</td>
<td>4 (10.3)</td>
</tr>
<tr>
<td>Laborers</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Employees</td>
<td>22 (56.4)</td>
</tr>
<tr>
<td>Others (housewives, students, etc.)</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td>Sun index</td>
<td></td>
</tr>
<tr>
<td>Sun exposure per week (hour), median (min-max)</td>
<td>24.8 (5.25–84)</td>
</tr>
<tr>
<td>Fraction of BSA exposed to sunlight, median (min-max)</td>
<td>0.20 (0.05–0.45)</td>
</tr>
<tr>
<td>Sun indexa median (min-max)</td>
<td>3.95 (1.1–23.52)</td>
</tr>
<tr>
<td>Seborrheic keratoses</td>
<td></td>
</tr>
<tr>
<td>Largest lesion diameter (mm), median (min-max)</td>
<td>2 (1–10)</td>
</tr>
<tr>
<td>Region, N (%)</td>
<td></td>
</tr>
<tr>
<td>Sun-exposed</td>
<td>38 (97.4)</td>
</tr>
<tr>
<td>Partially exposed</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Calcidiol</td>
<td></td>
</tr>
<tr>
<td>Calcidiol level (ng/ml), median (min-max)</td>
<td>14.3 (5.25–35.3)</td>
</tr>
<tr>
<td>Categoryb N (%)</td>
<td></td>
</tr>
<tr>
<td>Deficient (&lt;20 ng/ml)</td>
<td>28 (71.8)</td>
</tr>
<tr>
<td>Insufficient (20–29 ng/ml)</td>
<td>9 (23.1)</td>
</tr>
<tr>
<td>Normal (30–100 ng/ml)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Toxic (&gt;100 ng/ml)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

BMI = body mass index; BSA = body surface area.

*Hours of sun exposure per week × fraction of BSA exposed to sunlight

*According to Endocrine Society [37]

Table 2 describes the profile of energy, carbohydrate, fat, protein, and vitamin D intake among study participants. The vitamin D intake in the vitamin D deficient, insufficient, and normal group was 4.2 (0.10–30.10), 4.3 (2.0–28.80), and 15.55 (10.30–20.80) mcg/day (P = 0.226), respectively. Protein intake in subjects with insufficient and normal calcidiol levels was higher than in those with deficient calcidiol levels (54.25 [16.96] versus 48.28 [20.82], P = 0.234). The daily protein intake of subjects with deficient, insufficient, and normal calcidiol levels was 54.0 (12.10–89.0), 51.40 (26.0–76.0), and 67.25 (54.5–80.0) grams/day, respectively (P = 0.440).

Finally, we found that there was no significant correlation between the largest lesion diameter and SI (r = -0.057, P = 0.731) nor serum calcidiol (r = 0.108, P = 0.513). Exploratory analysis showed a weak negative correlation between lesion size and calcidiol level in the 19–39 years age group (r = -0.270, P = 0.250), and a significant positive correlation in the 40–59 years age group (r = 0.523, P = 0.018). There was also no significant correlation between calcidiol level and SI (r = 0.188, P = 0.253), vitamin D intake (r = 0.042, P = 0.801), or daily protein intake (r=0.113, p=0.495).
Table 2. Profile of energy, carbohydrate, fat, protein, and vitamin D intake

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Daily needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/day), median (min-max)</td>
<td>1189 (267–2357)</td>
<td>1800–2650 kcal/day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carbohydrate (%), mean (SD)</td>
<td>53.14 (11.11)</td>
<td>45–65%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fat (%), median (min-max)</td>
<td>31.57 (3.13–50.4)</td>
<td>20–30%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Protein (grams/day), median (min-max)</td>
<td>54 (12.10–89)</td>
<td>60–65 grams/day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin D (mcg/day), median (min-max)</td>
<td>4.3 (0.1–30.1)</td>
<td>15 mcg/day&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin D intake category, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficient</td>
<td>34 (87.2)</td>
<td></td>
</tr>
<tr>
<td>Sufficient</td>
<td>5 (12.8)</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.
<sup>a</sup>According to Indonesian Recommended Dietary Allowance 2019
<sup>b</sup>According to Indonesian Balanced Nutrition Guidelines

Conclusions

This study is among the first to describe the demographic and clinical characteristics of people living with SK in coastal areas of Indonesia and explore their SI, vitamin D intake, and serum calcidiol levels. Among this coastal population, we found no correlations between SI, calcidiol levels, and the size of the largest SK lesion. We also did not find any correlations between SI, vitamin D intake, and calcidiol levels.

Among our population, the median SI was greater than a similar study in Malaysia which found a median SI of 0.72 (0.26–1.28) in the urban population and 0.89 (0.42–1.83) in the rural population [20]. Nevertheless, despite the high SI, most of the subjects (71.8%) had vitamin D deficiency. This figure is within the reported prevalence of vitamin D deficiency in Southeast Asia, which ranges from 22%–87% [21-23]. We found that people with vitamin D deficiency were older and had higher BMIs. Older age is associated with decreased vitamin D metabolism due to decreased hepatic and kidney function [24], whereas in young age, vitamin D level is associated with higher vitamin D binding protein (DBP) levels, resulting in higher vitamin D levels [25]. Among overweight and obese individuals, vitamin D distribution into the fat tissue will reduce its total half-life and lower its serum level [26,27].

We originally hypothesized that lesion diameter would be associated with SI and calcidiol level. However, we found that there was no correlation between SI and SK largest diameter. The lesion size significantly increased along with the increment in age decades, as also found in the Korean population study. This finding might be caused by increased cumulative UV exposure in people with older age [28]. We also found no correlation between lesion diameter and calcidiol level. Vitamin D was found to play a role in the pathogenesis of SK in mice studies, including research on FGFR3, PIK3CA, and EGFR mutations. The topical administration of vitamin D analogs i.e. calcipotriol and tacalcitol, has been shown to reduce lesion size [29,30]. However, in the 19–39 years age group, there was a negative weak correlation between serum calcidiol level and the largest diameter, although this correlation was not significant. The opposite result was shown in individuals aged over 40 years, wherein we found a significant positive correlation between calcidiol levels and the largest diameter of SK. In this group, the higher the calcidiol, the larger the lesion size. We suspected that even though high sun exposure might cause higher calcidiol levels, it also increased the risk of SK, which was also a sign of photodamage.

We found that calcidiol level had no correlations with SI, even though the mean SI in subjects with insufficient and normal calcidiol was greater than in the deficient one. Moreover, there was an increment in calcidiol levels according to the increase in sun exposure duration. High sun exposure in the coastal community is among the many factors causing higher vitamin D levels in this community compared to the urban community. This finding is also similar to the study in England, which found that the average calcidiol levels of the population living closer to the coast were higher than in the people living within a radius of 40 km of the coastal area. But still, the high sun exposure (median 24.8 [5.25–84] hours per week) in the area with high UV index, did not prove to be adequate to increase calcidiol levels in this population. A study on a population of pregnant women in West Sumatra, Indonesia, also found that there was no relationship between outdoor activity and vitamin D deficiency, with an odds ratio of 0.986 (95% confidence interval: 0.972–1.001) [13].

There are also other factors affecting vitamin D production with the help of sunlight, including the amount of UV exposure, the use of sunscreen and protective clothing, and Fitzpatrick skin type [20]. Although food is not the primary source of vitamin D, the lack of vitamin D intake from food is one of several factors causing vitamin D deficiency in Indonesia [11,13]. The lack of vitamin D intake in subjects is
caused by the lack of food containing vitamin D consumption, including fish, shrimp, crab, milk, and dairy products. In our study, the mean vitamin D intake in the deficient group was lower than in the insufficient and normal levels groups. However, we found no correlation between vitamin D intake and calcidiol levels. Calcidiol levels are influenced by metabolizing enzymes and the polymorphisms of DBP-regulating genes and vitamin D receptor genes, which were beyond the scope of this study [24,31]. The VDR polymorphisms were found in a group of healthy women with vitamin D deficiency and insufficiency in North Sumatra, Indonesia [32].

In addition, the median intake of daily energy, carbohydrates, and protein was below the nutrient requirement. Protein intake, as one of the main nutrients, is thought to play a role in vitamin D deficiency. DBP is a protein derivative that transports 85%–88% of vitamin D in the blood [25,33]. To our knowledge, there is no known research subjecting protein intake to DBP formation and the influence of protein intake on vitamin D deficiency. In this study, the median protein intake was below the Indonesian 2019 recommended daily allowance. Protein intake in subjects with insufficient and normal vitamin D levels was higher than in deficient ones, but no correlation was found between protein intake and calcidiol levels.

Our study has several limitations. Firstly, this study did not compare subjects with SK and without SK in the coastal area. We also did not include the calculation of lesion number to shorten the examination time during the COVID-19 pandemic. Furthermore, our study utilized a 24-hour food questionnaire, which might be prone to recall bias and flat-rate. In addition, the median intake of daily energy, carbohydrates, and protein was below the nutrient requirement. Protein intake, as one of the main nutrients, is thought to play a role in vitamin D deficiency. DBP is a protein derivative that transports 85%–88% of vitamin D in the blood [25,33]. To our knowledge, there is no known research subjecting protein intake to DBP formation and the influence of protein intake on vitamin D deficiency. In this study, the median protein intake was below the Indonesian 2019 recommended daily allowance. Protein intake in subjects with insufficient and normal vitamin D levels was higher than in deficient ones, but no correlation was found between protein intake and calcidiol levels.

Our study has several limitations. Firstly, this study did not compare subjects with SK and without SK in the coastal area. We also did not include the calculation of lesion number to shorten the examination time during the COVID-19 pandemic. Furthermore, our study utilized a 24-hour food questionnaire, which might be prone to recall bias and flat-rate. In addition, the median intake of daily energy, carbohydrates, and protein was below the nutrient requirement. Protein intake, as one of the main nutrients, is thought to play a role in vitamin D deficiency. DBP is a protein derivative that transports 85%–88% of vitamin D in the blood [25,33]. To our knowledge, there is no known research subjecting protein intake to DBP formation and the influence of protein intake on vitamin D deficiency. In this study, the median protein intake was below the Indonesian 2019 recommended daily allowance. Protein intake in subjects with insufficient and normal vitamin D levels was higher than in deficient ones, but no correlation was found between protein intake and calcidiol levels.

In conclusion, we found low levels of serum calcidiol and vitamin D intake among people with SK living in the coastal area of Indonesia. There were no correlations between SI, calcidiol levels, and the size of the largest SK lesion, as well as correlations between SI, vitamin D intake, and calcidiol levels in this coastal population.

References

The Status of Dermoscopy in Chile: First National Study in Dermatologists

Juan Pablo Morales-Etcheberry¹, Francisco González-Coloma¹, Faustino Alonso-Traviesa², Nadia Vega-Almendra¹

¹ Department of Dermatology, Faculty of Medicine, University de Chile, Santiago de Chile, Chile
² Dermatology unit, San José Hospital, Servicio de Salud Metropolitano Norte, Santiago, Chile

Key words: dermoscopy, Chile, dermatologist, useful


Accepted: November 28, 2023; Published: April 2024

Copyright: ©2024 Morales-Etcheberry et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Juan Pablo Morales-Etcheberry, Ricardo Lyon #3443, Apt 1103, Ñuñoa, Chile.
E-mail: jpmoraleset@hotmail.com

ABSTRACT

Introduction: Scientific evidence supports dermoscopy as an essential tool in dermatological diagnosis.

Objectives: The objective is to know the factors that influence its use in Chilean dermatologists.

Methods: Analytical cross-sectional study. An adapted version of the survey was submitted from the pan-European study by Forsea et al to members of the Chilean Society of Dermatology, between September and December 2020. Analysis using descriptive statistics and multivariate analysis with ordinal logistic regression looking for factors associated with greater use of.

Results: One hundred and ninety-eight responses, mean age 46.3 years and 14.6 years on average practicing as dermatologists. 61.6% trained in dermoscopy during their residency. 98% use a dermatoscope. More than 80% consider dermoscopy useful for the diagnosis of melanomas, follow-up of melanocytic lesions, and diagnosis of pigmented and non-pigmented tumors. Between 50% and 70% consider it useful for monitoring non-melanocytic lesions, nail and hair pathologies. Greater confidence when evaluating pigmented and non-pigmented tumors and capillary pathology. Adjusting for age, sex, confidence, and education, participation in teaching was associated with greater use of dermoscopy in non-pigmented and pigmented tumors, and capillary pathology.

Conclusions: Percentage of participation in the survey and training in dermoscopy higher than in the reference study, recognizing the usefulness of dermoscopy for the diagnosis and follow-up of tumor pathologies. Participating in teaching is a strong independent factor that is associated with a greater use of dermoscopy in Chile. Dermoscopy is positioned as a tool widely used by Chilean dermatologists in their daily practice.
Introduction

Dermoscopy, also known as dermatoscopy, epiluminescence microscopy, or skin surface microscopy is a non-invasive, in-vivo technique that has traditionally been useful for the evaluation of suspicious skin lesions. Nowadays, dermoscopy main role has expanded beyond early detection of skin cancer, especially melanoma, becoming a routinely diagnostic and screening tool for several skin pathologies [1-3] including benign, inflammatory, infectious, and adnexal tumors. It is also useful to evaluate lesions on specific anatomical sites, such as mucosa and genitalia, and is helpful even on specific populations like afro-american and pediatric [4]. Recently, its usefulness has even been raised in the diagnosis of monkeypox [5].

In addition, the association of dermoscopy with some other technologies adds new development possibilities, such as super high magnification optical dermoscopy [6], teledermoscopy [7], ex vivo dermoscopy [8] and artificial intelligence-assisted diagnosis [9].

Nevertheless, not all dermatologists use dermoscopy on a daily basis, and several studies have attempted to explain this phenomenon, highlighting among the reasons the limited access to dermoscopes and the lack of training in dermoscopy during residency and continuing education programs [10-15].

There are no similar studies in Chile that allow us to acknowledge the variables of dermoscopy use within the country.

Objectives

The objective of this paper is to characterize dermoscopy use among national dermatologists and clarify the main obstacles to expand its implementation.

Methods

An analytical cross-sectional study was carried out. The sample corresponded to all the registered dermatologists of the Chilean Society of Dermatology (SOCHIDERM), which is the only scientific organization that brings together 70% of dermatologists in Chile, with 453 members in 2020. The instrument used to collect the information was created based on the Eurodermoscopy working group questionnaire (Drs. Ana-Maria Forsea, Alan C Geller, Giuseppe Argenziano, Veronique del Marmol, Iris Zalaudek and Peter H. Soyer) in accordance with International Dermoscopy Society (IDS) guidelines and adapted to Spanish language by Dr. Susana Puig. A cross-cultural adaptation was also carried out to modify the questionnaire to Chilean Spanish, without altering the content of the questions. Formal authorization was requested from the authors of the questionnaire for its use.

The final questionnaire was transcribed into a digital version using the Google Forms tool.

The original questionnaire was composed of twenty short-answer and multiple-choice questions that inquire demographic and clinical practice characteristics of the subjects, their formal education and experience with the dermatoscope, their opinion about its usefulness and their self-confidence in the use of this tool. Three questions were added to the original questionnaire: “How many minutes on average do you have for each consultation?”, “In what area of dermatology do you usually work?” and “Age of dermatological patients attended”. The instrument did not include questions that would allow participants to be identified.

The survey was distributed by email and could be completed on a computer or mobile phone if there was an internet connection. The questionnaire allowed only one answer per dermatologist, and it was not possible to be sent unless all the questions were answered. At question number twelve (“Do you use dermoscopy?) only those who answered “yes” were able to access the following questions related to the use of dermoscopy in clinical practice, and those who answered “no” accessed a new section of the questionnaire in which the reasons for not using this technique were inquired. The questionnaire was available between September 2020 and December 2020, during which time an email reminder was sent once a month to all dermatologists in the database. The answers were compiled by Google Forms as they were obtained in a spreadsheet.

An exploratory analysis of the database was carried out, identifying missing values and distribution of the variables. Subsequently, averages and standard deviations were calculated for the quantitative variables, and absolute and relative frequencies for the qualitative ones. Finally, an ordinal logistic regression model was built to identify factors associated with the use of dermoscopy in the different groups of pathologies. Analyzes were performed in STATA 16.1. Statistically significant was defined as obtaining a P value less than 0.05.

Results

Of the initial sample of 453 surveys sent, a total of 198 (43.71%) were answered and 255 were unanswered. All the answered surveys were considered in the analysis of the data. The demographic and clinical practice characteristics of the participants are described in Tables 1 and 2. Of the dermatologists surveyed, 122 (61.6%) reported having received training in dermoscopy during their residency. It should be noted that the average age of this group is 38.8 years (standard deviation [SD] 6.9), while the average age of those who state that they have not received formal education during their residency is 58.1 years (SD 8.9), difference being statistically
significant (P < 0.0001). In addition to residency, those surveyed indicate attendance at congresses (93.9%), books on the subject (80.3%) and face-to-face courses (61.6%) as the main source of training in dermoscopy. Only 6 of those surveyed (3%) stated that they did not have any type of training in dermoscopy.

Of the total respondents, 4 (2%) did not use dermoscopy, whose average age is 69.5 years (SD 3.3), with no differences by gender. When asked the reasons that lead them to not use dermoscopy, 3 of them stated that they do not have enough confidence in their abilities and 1 did not considered it useful for clinical practice.

Of the total number of respondents, 98% used dermoscopy, and have been using this technique for an average of 10.6 years (SD 6.1). The majority used polarized light dermoscopy (90.9%), followed by non-polarized light (32.3%) and digital camera dermoscopy (24.8%). Videodermoscopy was used by 13.1% of those surveyed.

Regarding the different clinical diagnosis in which dermoscopy was found to be useful, the results are shown in Table 3. There was unanimous agreement in the usefulness of this tool for the diagnosis of melanoma (100%) and

Table 1. General characteristic of the surveyed (Part 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>99 (50%)</td>
</tr>
<tr>
<td>• Female</td>
<td>99 (50%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>• Average age</td>
<td>46.3 years (SD 12.2)</td>
</tr>
<tr>
<td>• Age range</td>
<td>28 – 74 years</td>
</tr>
<tr>
<td>• Average male age</td>
<td>46.3 years (SD 12.4)</td>
</tr>
<tr>
<td>• Average female age</td>
<td>46.4 years (SD 12.2)</td>
</tr>
<tr>
<td><strong>Workplace</strong></td>
<td></td>
</tr>
<tr>
<td>• Private personal practice</td>
<td>96 (48.5%)</td>
</tr>
<tr>
<td>• Medical center</td>
<td>83 (41.9%)</td>
</tr>
<tr>
<td>• Private clinic</td>
<td>93 (47%)</td>
</tr>
<tr>
<td>• Public hospital</td>
<td>95 (48%)</td>
</tr>
<tr>
<td>• Resident teaching</td>
<td>86 (43.4%)</td>
</tr>
<tr>
<td>• Other</td>
<td>3 (1.52%)</td>
</tr>
<tr>
<td><strong>Number of years as a dermatologist</strong></td>
<td></td>
</tr>
<tr>
<td>• Average</td>
<td>146.6 years (SD 12.5)</td>
</tr>
<tr>
<td>• Range</td>
<td>0 – 47 years</td>
</tr>
</tbody>
</table>

SD = standard deviation.

Table 2. General characteristic of the surveyed (Part 2).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average number of patients attended per month</strong></td>
<td></td>
</tr>
<tr>
<td>• Less than 150 patients</td>
<td>27 (13.64%)</td>
</tr>
<tr>
<td>• Between 150 and 300 patients</td>
<td>88 (44.44%)</td>
</tr>
<tr>
<td>• Between 300 and 450 patients</td>
<td>64 (32.32%)</td>
</tr>
<tr>
<td>• More than 450 patients</td>
<td>19 (9.6%)</td>
</tr>
<tr>
<td><strong>Average consult time per patient</strong></td>
<td>19.3 minutes (SD 5.3)</td>
</tr>
<tr>
<td>• 15 minutes</td>
<td>83 (41.9%)</td>
</tr>
<tr>
<td>• 20 minutes</td>
<td>80 (40.4%)</td>
</tr>
<tr>
<td>• 30 minutes</td>
<td>28 (14.1%)</td>
</tr>
<tr>
<td><strong>Area of practice in dermatology</strong></td>
<td></td>
</tr>
<tr>
<td>• General dermatology</td>
<td>171 (86.4%)</td>
</tr>
<tr>
<td>• Pediatrics</td>
<td>55 (27.8%)</td>
</tr>
<tr>
<td>• Acne and rosacea</td>
<td>101 (51.0%)</td>
</tr>
<tr>
<td>• Psoriasis</td>
<td>70 (35.4%)</td>
</tr>
<tr>
<td>• Esthetic</td>
<td>51 (25.8%)</td>
</tr>
<tr>
<td>• Oncology</td>
<td>88 (44.4%)</td>
</tr>
<tr>
<td>• Psychodermatology</td>
<td>11 (5.6%)</td>
</tr>
<tr>
<td>• Other</td>
<td>24 (12.6%)</td>
</tr>
<tr>
<td><strong>Percentage of adult and pediatric patients seen per month</strong></td>
<td></td>
</tr>
<tr>
<td>• 100% adults</td>
<td>29 (14.5%)</td>
</tr>
<tr>
<td>• 75% adults and 25% pediatrics</td>
<td>145 (72.5%)</td>
</tr>
<tr>
<td>• 50% adults and 50% pediatrics</td>
<td>20 (10.0%)</td>
</tr>
<tr>
<td>• 25% adults and 75% pediatrics</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>• 100% pediatrics</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td><strong>Average number of skin cancer patients seen per month</strong></td>
<td></td>
</tr>
<tr>
<td>• Less than 5%</td>
<td>83 (41.5%)</td>
</tr>
<tr>
<td>• Between 5 and 15%</td>
<td>71 (35.5%)</td>
</tr>
<tr>
<td>• Between 15 and 30%</td>
<td>28 (14.0%)</td>
</tr>
<tr>
<td>• More than 30%</td>
<td>18 (9.0%)</td>
</tr>
</tbody>
</table>
pigmented tumors (100%). It was also considered to be useful for non-pigmented tumors (86.1%), monitoring melanocytic lesions (99%), follow-up of non-melanocytic lesions (54.6%), the evaluation of hair pathologies (68%) and to evaluate nail pathologies (57.7%). In the diagnosis of inflammatory lesions, the respondents considered it useful in 35% and somewhat useful by 53.1% of them.

When asking the subjects about dermoscopy use frequency according to the type of lesion, the most of them referred using it in more than 70% of cases of pigmented tumors, non-pigmented tumors and hair pathologies, being less used in inflammatory and nail pathologies (Table 4).

Regarding the use of diagnostic algorithms for pigmented lesions, pattern analysis ranks first with 70.2%, followed by ABCD with 34.9% and those that do not use any algorithm with 26.8%. It should be noted that 43.9% of those surveyed used more than one algorithm.

The respondents stated that they were confident in their dermoscopy skills to evaluate pigmented tumors (89.7%), non-pigmented tumors (79.4%) and hair pathology (52.1%). The degree of confidence was lower when evaluating inflammatory and nail lesions (Table 5).

The main advantages of using dermoscopy, according to those surveyed are the diagnosis of melanomas in early stages (93.3% strongly agree), the follow-up of lesions (89.7% strongly agree), the increase in the confidence on the clinical diagnosis (83.5% strongly agree) and the reduction in the number of unnecessary biopsies/excisions (77.3% strongly agree). It is noteworthy that, when asking for an increase in remuneration associated with the use of dermoscopy, 28.9% state that they disagree and 36.6% state that they strongly disagree. The rest of the results associated with the advantages of dermoscopy are presented in Table 6.

Of those surveyed, 94.8% believed that using dermoscopy has increased the number of detected melanomas compared to a naked eye examination, and 78.9% believe that it has reduced the number of excisions of benign lesions.

After adjusting for age, sex, confidence, and education, being involved in teaching was associated with greater use of dermoscopy in non-pigmented tumors, with an OR 2.8

### Table 3. Usefulness of dermoscopy in different areas of dermatological care.

<table>
<thead>
<tr>
<th>Area</th>
<th>Useful</th>
<th>Somewhat useful</th>
<th>Not useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of melanoma</td>
<td>194 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up of melanocytic lesions</td>
<td>192 (99%)</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis of non-pigmented skin tumors</td>
<td>194 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis of inflammatory skin lesions</td>
<td>167 (86.1%)</td>
<td>24 (12.4%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>Diagnosis of pigmented skin tumors</td>
<td>68 (35.0%)</td>
<td>103 (53.1%)</td>
<td>23 (11.9%)</td>
</tr>
<tr>
<td>Follow-up of non-melanocytic skin lesions</td>
<td>106 (54.6%)</td>
<td>69 (35.6%)</td>
<td>19 (9.8%)</td>
</tr>
<tr>
<td>Diagnosis and follow-up of hair disorders</td>
<td>132 (68.0%)</td>
<td>52 (26.8%)</td>
<td>10 (5.2%)</td>
</tr>
<tr>
<td>Diagnosis and follow-up of nail disorders</td>
<td>112 (57.7%)</td>
<td>63 (32.5%)</td>
<td>19 (9.8%)</td>
</tr>
</tbody>
</table>

### Table 4. Frequency of use of dermoscopy according to diagnostic groups.

<table>
<thead>
<tr>
<th>Area</th>
<th>&lt;10%</th>
<th>11%-30%</th>
<th>31%-50%</th>
<th>51%-70%</th>
<th>&gt;70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmented skin tumors</td>
<td>2 (1%)</td>
<td>1 (0.5%)</td>
<td>15 (7.7%)</td>
<td>18 (9.3%)</td>
<td>158 (81.5%)</td>
</tr>
<tr>
<td>Non-pigmented skin tumors</td>
<td>5 (2.6%)</td>
<td>7 (3.6%)</td>
<td>17 (8.8%)</td>
<td>28 (14.4%)</td>
<td>137 (70.6%)</td>
</tr>
<tr>
<td>Inflammatory skin lesions</td>
<td>24 (12.4%)</td>
<td>22 (11.3%)</td>
<td>44 (22.7%)</td>
<td>52 (26.8%)</td>
<td>52 (26.8%)</td>
</tr>
<tr>
<td>Hair disorders</td>
<td>14 (7.2%)</td>
<td>19 (9.8%)</td>
<td>29 (15%)</td>
<td>26 (13.4%)</td>
<td>106 (54.6%)</td>
</tr>
<tr>
<td>Nail disorders</td>
<td>22 (11.4%)</td>
<td>21 (10.8%)</td>
<td>41 (21.1%)</td>
<td>36 (18.6%)</td>
<td>74 (38.1%)</td>
</tr>
</tbody>
</table>

### Table 5. Confidence level in dermoscopic diagnostic skills.

<table>
<thead>
<tr>
<th>Area</th>
<th>Trust</th>
<th>Somewhat trust</th>
<th>Does not trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmented skin tumors</td>
<td>174 (89.7%)</td>
<td>19 (9.8%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Non-pigmented skin tumors</td>
<td>154 (79.4%)</td>
<td>34 (17.5%)</td>
<td>6 (3.1%)</td>
</tr>
<tr>
<td>Inflammatory skin lesions</td>
<td>64 (33%)</td>
<td>96 (49.5%)</td>
<td>34 (17.5%)</td>
</tr>
<tr>
<td>Hair disorders</td>
<td>101 (52.1%)</td>
<td>74 (38.1%)</td>
<td>19 (9.8%)</td>
</tr>
<tr>
<td>Nail disorders</td>
<td>80 (41.2%)</td>
<td>88 (45.4%)</td>
<td>26 (13.4%)</td>
</tr>
</tbody>
</table>
however, not all of them continue in professional practice. Our convenience sample could have had an overrepresentation of young dermatologists, since it is a survey sent over the Internet, which could be unfriendly to older dermatologists who are less experienced in the use of technology. However, our sample average age was only 9 years compared to the average age of SOCHIDERM dermatologists and a similar percentage of men and women. On the other hand, it could be argued that this type of survey is usually answered by professionals with an interest in dermoscopy rather than by those who are sporadic users or who simply do not use it. This pioneer study in Chile and Latin America shows that, nowadays, dermoscopy is widely used among Chilean dermatologists in a daily basis and beyond the diagnosis and follow-up of malignant skin pathology, expanding to other aspect of the dermatological practice. Nevertheless, it is important to look for new strategies to increase the adherence of this technique among dermatologists and to increase confidence in all areas of clinical practice. Videodermoscopy is a tool that is still under-used, possibly due to its lower access and associated cost.

Even if there are similar study worldwide that try to describe the use of dermoscopy in different countries and, in fact, the Spanish version of the study by Forsea et al was used to carry out our work with only a few minor changes, this is the first study in Chile to characterize the Chilean dermatologist population and its pattern of use of dermoscopy. On the other hand, the replication of the survey from the pan-European study allowed us to use a validated instrument and be able to make comparisons more easily with international experiences.

Conclusions

There was a 43.71% participation between the SOCHIDERM dermatologist, a higher percentage than the reference pan-European study with an average response rate of 33.2% among the participating countries [10]. In our sample, we have a lower percentage of non-users of this technique, compared to 11% in the reference study, with a very high percentage of use of this tool, consistent with other similar reports [11]. Its use was especially high in benign and malignant melanocytic lesions and pigmented tumors, similar to what is described in the European study. In the study by Forsea et al, 40% of the dermatologists had training in dermatology during their residency, a result similar to the finding in our survey. Also, similar results were found regarding the use of digital dermoscopy, reaching 38% of use. Participation in teaching activities arises with a factor that is associated with a greater use of this technique.

The main reason for not using digital dermoscopy among our respondents was a lack of confidence in their abilities, while the pan-European study revealed a lack of training on the subject as the main cause.

Our work has limitations in relation to its design, methodology and proportions. The main limitation of this study is the composition of the sample, since it is a convenience sample, which, despite the large sample size, does not ensure the representativeness of the results for all dermatologists in Chile. Although SOCHIDERM, the only association in the area in the country, brings together most dermatologists in Chile, 30% of the country specialists were not contacted for the application of the survey. In its records, it mentions an average age for its partners of 55 years, with 56.07% women, however, not all of them continue in professional practice. Our convenience sample could have had an overrepresentation of young dermatologists, since it is a survey sent over the Internet, which could be unfriendly to older dermatologists who are less experienced in the use of technology. However, our sample average age was only 9 years compared to the average age of SOCHIDERM dermatologists and a similar percentage of men and women. On the other hand, it could be argued that this type of survey is usually answered by professionals with an interest in dermoscopy rather than by those who are sporadic users or who simply do not use it.

This pioneer study in Chile and Latin America shows that, nowadays, dermoscopy is widely used among Chilean dermatologists in a daily basis and beyond the diagnosis and follow-up of malignant skin pathology, expanding to other aspect of the dermatological practice. Nevertheless, it is important to look for new strategies to increase the adherence of this technique among dermatologists and to increase confidence in all areas of clinical practice. Videodermoscopy is a tool that is still under-used, possibly due to its lower access and associated cost.

Even if there are similar study worldwide that try to describe the use of dermoscopy in different countries and, in fact, the Spanish version of the study by Forsea et al was used to carry out our work with only a few minor changes, this is the first study in Chile to characterize the Chilean dermatologist population and its pattern of use of dermoscopy. On the other hand, the replication of the survey from the pan-European study allowed us to use a validated instrument and be able to make comparisons more easily with international experiences.

References


Importance of the C-Reactive Protein to Albumin Ratio in the Diagnosis and Prognosis of Mycosis Fungoides

Gamze Taş-Aygar¹, Hatice Ataş¹, Müzeyyen Gönuğ¹, Selda Pelin Kartal¹

¹ University of Health Sciences, Etlik City Hospital, Dermatology Clinic, Ankara, Turkey

Key words: Mycosis Fungoides, diagnosis, CRP, albumin

Citation: Taş-Aygar G, Ataş H, Gönuğ M, Kartal SP. Importance of the C-Reactive Protein to Albumin Ratio in the Diagnosis and Prognosis of Mycosis Fungoides. Dermatol Pract Concept. 2024;14(2):e2024097. DOI: https://doi.org/10.5826/dpc.1402a97

Accepted: November 18, 2023; Published: April 2024

Copyright: ©2024 Taş-Aygar et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Taş-Aygar Gamze, University of Health Sciences, Etlik City Hospital, Dermatology Clinic, Ankara, Turkey, E-mail: gamze_0890@hotmail.com.

ABSTRACT

Introduction: The C-reactive protein to albumin ratio (CAR) lately has demonstrated as a prognostic factor and an indicator of disease activity, severity and prognosis in solid organ malignancies and inflammatory diseases. However, the effects of CAR have not been investigated in mycosis fungoides (MF) patients yet.

Objectives: This study aimed to determine the potential role of CAR as a diagnostic and a prognostic indicator in MF.

Methods: We retrospectively investigated the electronic medical records of 97 patients with MF admitted to the Dermatology Clinic of Health Sciences University, Diskapi Yildirim Beyazit Training and Research Hospital between January 2014 and December 2020. In total, 60 patients with MF were enrolled in the study. CAR was evaluated, patient and control group. Also, the other clinicopathological factors including age, lactate dehydrogenase, stage of disease, beta-2-microglobulin levels, and sedimentation levels were evaluated.

Results: The median value of CAR was 0.85 (0.10-7.51) in the patient group, whereas it was 0.39 (0.0-1.11) in the control group (P < 0.001). Patients with disease progression (N = 16, 13M, 3 F) had a median value of CAR 0.84 (0.10-7.51) and the median value of CAR (N = 44) was 0.86 (0.12-4.57) in the group of patients with stable disease. The CAR value had no prognostic significance (P > 0.05).

Conclusions: There is no association between the CAR and progression in the stage in MF patients. But the CAR is significantly higher in patients with MF than in the control group. The CAR can be a guide for us in cases where we have difficulty in diagnosing.
Introduction

Primary cutaneous lymphomas are a heterogeneous group of extranodal non-Hodgkin lymphomas. Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphomas (CTCL) caused by malignant proliferation of clonal T lymphocytes in the skin. MF was generally affecting older patients with the median age at diagnosis between 55 and 60 years old and affecting more men than women. The children can also be affected by this lymphoma. The disease usually begins as brownish erythematous patches in sun-protected areas and progresses slowly over the years, and in some patients may remain in the same stage for years without progress. Currently, there is no cure for MF and symptomatic treatment is given especially in early-stage disease. While it is aimed to increase the quality of life in early-stage patients, it is aimed to increase life expectancy in advanced stage patients. The main treatment of early-stage disease is skin-directed treatments (topical corticosteroids and phototherapy). When the disease progresses to advanced stages, systemic therapy including systemic chemotherapy is applied and the disease can be fatal [1-4]. Therefore, to diagnose the disease and anticipating the prognosis is an important need.

An indicator that informs the prognosis of the disease and provides information about the severity of the disease can be useful in making treatment decisions in complex cases.

C-reactive protein (CRP) to albumin ratio (CAR) was calculated as the ratio of serum CRP level (mg/L) to serum albumin level (g/dL), which were obtained from the biochemistry profile. CAR is a novel inflammation-based prognostic score and an inflammation biomarker in inflammatory processes. CAR is associated with poor outcomes and severity of inflammation in various diseases, such as psoriasis, cardiovascular diseases, ischemic stroke, sepsis, acute pancreatitis, uveitis, Takayasu arteritis, and cancers. CAR has higher diagnostic accuracy than C-reactive protein alone [5-13]. CAR has been considered as a valuable indicator of inflammatory status and prognosis in cancers, it has not been evaluated in patients with MF.

Objectives

In this investigation, our aim was to assess the applicability of the CAR value, readily and inexpensively derived from blood parameters, in both diagnosing and prognosticating MF disease.

Methods

We reviewed the files of MF patients in the Dermatology Clinic of Health Sciences University, Diskapi Yildirim Beyazit Training and Research Hospital between January 2014 and December 2020. A total of 97 patients were retrieved initially, 37 were excluded from the study due to lack of follow-up and insufficient laboratory values. The study enrolled all patients aged 18 and over who had available data. Inclusion criteria include being diagnosed with MF clinically and histopathologically, and no history of inflammatory disease and malignancy (non-MF). All our patients had not yet received treatment when they were included in the study. Data on age, sex, duration, onset age and stage of disease, serum biochemistry profile, including serum CRP, albumin, lactate dehydrogenase (LDH) and beta2 microglobulin levels and complete blood count, were collected. Blood samples were taken from all patients under the same conditions in our hospital laboratory. TNMB and histopathological staging of the cases were performed in accordance with International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) criteria at the time of peripheral blood sampling, retrospectively.

Healthy volunteers who underwent routine physical examination in our hospital were taken as the control group. The patient and control groups were matched in terms of age and gender. Persons who had other autoimmune diseases, liver or kidney disease, hematologic disease, diabetes, cancer, acute or chronic infections were excluded from the study.

Disease progression was considered as tumor development and transition to advanced stages (stage IIB and above). Because with tumor development, the disease transforms from early stage to advanced stage disease. Tumor stage and above stages are considered advanced stage disease in MF(2). In this study, 3 of our patients were in stage IIA at the time of diagnosis, but subsequently showed tumor formation through their plaques and progressed to stage IIB. At the same time, those who were initially in the advanced stage group but showed improvement and moved to the early-stage group were included in the "good prognosis" group. We have 2 patients with this situation. The tumors of patients who were initially Stage IIB regressed clinically and pathologically and progressed to the plaque stage. One of these patients is directly followed as stage IB because there is no lymph node involvement. The other patient is followed as stage IIA. In our clinic, file records of all our patients are kept meticulously. The disease prognoses of all patients included in the study were examined one by one and recorded. Patients who are at an advanced stage and whose disease does not regress are not included in the "good prognosis" group.

The data obtained were transferred to the computer environment and evaluated with the SPSS (v.15.0) statistics package program. The compliance of the data to normal distribution was evaluated with the Kolmogrov Smirnov test.

This study was approved by the tertiary hospital ethics committee. Written informed consent was obtained from all participants.
Results

The study group consisted of a total of 120 people, including 60 MF (28 female, 32 male) patients and 60 (28 female, 32 male) control group. Patient age ranged from 20 to 83 years (51.95±13.64). There was no difference in age and gender between control and patient groups in the study (P > 0.05 for each). Based on ISCL/EORTC staging, 9 patients (15%) were stage IA, 2 (3.3%) were stage IB, 34 (56.7%) were stage IIA, 6 (10.0%) were stage IIB, 7 (11.7%) were stage IIIB, 1 (1.65%) was stage IVA1 and 1 (1.65%) was stage IVA2.

The median value of CAR was 0.91 (0.12-7.51) in the patient group, whereas it was 0.39 (0.0-1.11) in the control group. There was a statistically significant difference between groups (P < 0.001). There was a statistically significant difference in sedimentation, CRP, albumin and eosinophil levels between patient and control groups (Table 1).

Patients were first evaluated according to stages. In stage I (T1, T2), there are patients with only skin findings without involvement of any other area. Stage I is divided into two: Stage IA and Stage IB. T1 represents patients with patches and/or plaques covering <10% of the body. However, since the tumor burden of patches and plaques is not the same, this stage is divided into two as T1a and T1b in the final classification (14). T1a consists of patches only, while T1b consists of plaques ± patches. These patients are also considered stage IA. T2 represents patients with patches and/or plaques in >10% of the body. T2a consists of patches only, while T2b consists of plaque ± patches. There was not a statistically significant difference between the CAR values of the patients, stages, and those with only skin involvement and those with lymph node and systemic involvement (Table 2).

16 patients had progressive disease (13M, 3 F). Lymphocyte count, sedimentation, LDH and Beta2 microglobulin were found to be associated with poor prognosis in these patients. Patients with disease progression (N = 16) had a median value of CAR 0.94 (0.42-7.51) and the median value of CAR (N:44) was 0.91 (0.12-4.57) in the group of patients without disease progression. The CAR value had no prognostic significance (P > 0.05) (Table 3).

Conclusions

MF, the most common CTCL, is characterized by the clonal proliferation of skin homing mature T-cells in chronically inflamed skin lesions. Malignant T-cells create a chronic inflammatory environment in which they take control of the inflammatory environment, suppressing cellular immunity and anti-tumor responses, while fostering their own expansion [15]. The median time from onset of symptoms to diagnosis is 3 to 4 years, also it can be decades. Clinico-pathological correlation is necessary for the diagnosis of MF. Making the diagnosis is difficult for both the pathologist and the clinician because the findings are non-specific. Classical form of MF presents as persistent, progressive erythematous
patches or plaques of variable size and shape, which have a scaly atrophic surface, located on sun-protected areas. MF can appear in many clinical forms, except for the classic patch-plaque-tumor type. Due to the atypical types of MF, the list of diseases in the differential diagnosis of MF is quite extensive. This is why the MF is known as the "great imitator" [1,3,16]. In cases where there is no clinical and pathological agreement on the diagnosis of MF, multiple biopsies should be taken from the lesions at regular intervals. The patient should be informed and should not be excluded from follow-up.

The degree of skin involvement and the presence of extracutaneous disease are the most important criteria for long-term life expectancy in MF. Therefore the TNMB (tumor, node, metastasis, blood) staging remains an important prognostic factor in MF. This classification has 9-level and early stage includes stages IA, IB and IIA. Other stages known as advanced or tumor stage. MF may remain stable or may progress to an advanced stage or a Sezary syndrome. Although the disease progresses with a poor prognosis in advanced stages, patients with MF having T1 stage have a similar life expectancy to that of control populations [2,17]. In addition, factors such as male gender, older age, histopathological type (folliculotropic MF, poor prognostic), large cell transformation, high serum beta2-microglobulin and lactate dehydrogenase LDH levels, and peripheral eosinophilia have been shown to be important in prognosis. Recently, the high neutrophil-lymphocyte ratio has been added to this list [2,18,19]. Our study also confirmed previous findings and concluded that the beta2 microglobulin, sedimentation and LDH is associated with a poor prognosis [20]. Anticipating prognosis in patients may be important in terms of close follow-up of patients and therapies to be selected.

CRP is a positive acute-phase reactant secreted by the liver during the inflammatory processes. Multiple studies have demonstrated that elevated serum CRP levels are associated with a poor prognosis for various solid tumors and lymphomas [21-23]. We also found that CRP levels were significantly higher in patients with MF than in the control group. Also, albumin is a negative acute-phase protein synthesized by the liver and reflects the nutrition status of the host. Pretreatment serum albumin level is a known prognostic marker of several solid malignancies and several hematological malignancies [24-26]. Therefore, CAR, a combined model of both CRP and albumin, demonstrated the outcome of the disease in some diseases better than either would show individually [5-11]. In addition the usability of CAR, an inexpensive parameter that can be easily calculated from the biochemistry profile, was evaluated in our study. In this study, we found the median CAR value significantly higher in patients with MF than in the control group. As we mentioned before, it can take years to make a definitive diagnosis of MF. We think that the CAR can be used as an additional indicator to guide us in the direction of MF in patients with suspected MF. We suggest that in patients with suspected MF, those with high CAR should be followed more closely.

Since CAR has been used as an indicator of inflammation, its use in the assessment of severity and activity of diseases involving the skin such as psoriasis and Behcet disease. It has been shown that the CAR value in psoriasis patients decreased significantly after treatment with a biologic agent. Thus, it has been shown that CAR can be a good indicator.

### Table 3. Distribution of patients in the study group according to variables thought to be related to their prognosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Poor prognosis (N = 16)</th>
<th>Good prognosis (N = 44)</th>
<th>t-test; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta2 microglobulin</td>
<td>2.40 (1.53-4.09)</td>
<td>1.96 (1.18-3.77)</td>
<td>2.281; 0.023</td>
</tr>
<tr>
<td>CRP</td>
<td>3.72 (1.70-26.0)</td>
<td>3.89 (0.50-19.0)</td>
<td>0.478; 0.633</td>
</tr>
<tr>
<td>Sedimentation</td>
<td>4.00 (0.0-29.0)</td>
<td>11.0 (2.0-41.0)</td>
<td>2.079; 0.038</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.43 (3.38-4.9)</td>
<td>4.5 (3.48-5.08)</td>
<td>0.831; 0.406</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>2.87 (0.82-15.60)</td>
<td>1.99 (0.00-4.87)</td>
<td>0.157; 0.878</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>200.0 (10.0-1400.0)</td>
<td>200.0 (10.0-2610.0)</td>
<td>0.241; 0.809</td>
</tr>
<tr>
<td>CAR</td>
<td>0.94 (0.42-7.51)</td>
<td>0.91 (0.12-4.57)</td>
<td>0.301; 0.763</td>
</tr>
<tr>
<td>N/L</td>
<td>2.87 (0.82-15.60)</td>
<td>1.99 (0.0-4.87)</td>
<td>1.639; 0.101</td>
</tr>
<tr>
<td>Disease duration</td>
<td>3.0 (1.0-21.0)</td>
<td>4.0 (0.50-35.0)</td>
<td>0.575; 0.565</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1800.0 (500.0-4000.0)</td>
<td>2100.0 (1000.0-4860.0)</td>
<td>2.124; 0.046</td>
</tr>
<tr>
<td>Platelet</td>
<td>230.0 (128.0-418.0)</td>
<td>271.0 (187.0-406.0)</td>
<td>1.298; 0.210</td>
</tr>
<tr>
<td>LDH</td>
<td>214.0 (173.0-399.0)</td>
<td>187.0 (145.0-403.0)</td>
<td>2.684; 0.007</td>
</tr>
</tbody>
</table>

CAR = CRP to Albumin Ratio; CRP = C Reactive Protein; LDH = lactate dehydrogenase; N/L:Neutrophil to Lymphocyte ratio.
of the severity of systemic inflammation in psoriasis [8]. It has been shown that in patients with chronic uveitis such as Behcet disease, CAR may be a marker for acute uveitis. CAR is an important parameter in determining the activation of the uveitis and correlated with the severity of intraocular inflammation in uveitis [12,13].

The prognostic value of CAR and its association with the advanced tumor have been established quite clearly in various solid organ tumors recently. The prognostic importance of CAR value in pancreatic cancer, which is one of the cancers with the poor prognosis, has been investigated many times. It has been shown that the CAR value increases in advanced disease and it has been reported that the CAR value is associated with prognosis. The CAR value is also shown to be useful in monitoring the effectiveness of chemotherapy in pancreatic cancer [7,27-29]. In a study conducted in 200 patients with newly diagnosed non-metastatic breast cancer, it was shown that increased CAR rate is associated with a high risk of recurrence or death in patients with breast cancer. In addition, the cut-off value was found to be lower in studies conducted in breast cancer compared to studies in other malignancies. It was interpreted that the cut-off value increased as more patients with advanced disease were included in the study [30]. In another study, high CAR was significantly associated with short-term survival prognosis of terminal cancer patients [31]. In a study in which 192 patients with acute pancreatitis were evaluated; The CAR was found to be the prognostic score in acute pancreatitis [9]. In our study, there was no association with CAR value and prognosis.

We compared the CRP, albumin, and CAR values with the control group, we found a significant difference in MF. But we did not find any of the CRP, albumin, and CAR values associated with prognosis. It well known that the prognosis of patients with cancer is associated with the clinical stage of cancer. MF is T-cell skin lymphoma. The prognosis is good unless there is systemic involvement. Especially distant metastases and the development of Sezary syndrome (advanced stage disease) are the main reasons that shorten the life span. Only one of our patients had Sezary syndrome, and one had N2 lymph node involvement. Systemic metastasis was not observed in any of the patients. While designing the study, we also considered tumor development and transition to advanced stages as poor prognosis. However, while tumor development detected 15% of our patients, none of these patients progressed to stage 4, which is systemic involvement. Also in a study conducted in patients with pancreatic cancer, it was shown that CAR has prognostic importance only in stage 3-4 (advanced stage) patients [27]. These reasons may have caused that CRP, Albumin, and CAR values were not related to prognosis in MF.

There were several limitations to our study. Possible missing data due to being a retrospective study. The collection of variables from a small group of patients at a single center makes it difficult to generalize these results to the general population. In our study, the number of patients classified as IIA is higher. Most stage I patients can be followed up in external centres with other diagnoses due to diagnostic difficulties. Since the possibility of systemic involvement is low in stage I disease, they can be followed up by physicians in secondary care hospitals. Since our center is a 3rd step treatment center, there are few stage I patients. Stage III disease is a rare stage. Therefore, there are few erythrodermic patients in our study group. Stage IV patients are followed up by hematology because they represent advanced stage and metastatic patient group. However, this does not reduce the reliability of our study. As it is known, only skin involvement occurs in stage I disease. In a disease that is very difficult to diagnose in the early stage, elevated systemic markers are not expected because systemic involvement is not common. Additional prospective studies with larger patient populations and with a predominance of advanced-stage patients, involving multiple centers are required to evaluate the CAR as a prognostic predictor.

Although CAR has been demonstrated to have a prognostic role in various solid malignancies and inflammatory diseases, it seems that there is no association between the CAR and progression in stage in MF patients. But the CAR is significantly higher in patients with MF than in the control group. The CAR can be a guide for us in cases where we have difficulty in diagnosing.

References

6. Aseringeck Akkecci N, Yildirim Cetin G, Gogebakan H, Acipayam C. The C-Reactive Protein/Albumin Ratio and Complete Blood Count Parameters as Indicators of Disease Activity in
Dermoscopy Use in Africa: Determinants and Challenges

Enechukwu Nkechi Anne 1, Adebola O Ogunbiyi2, Awatef Kelati3, Ahmed Sadek4, Ibrahima Traoré5, Daudi Mavura6-7

1 Nnamdi Azikiwe University/Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria
2 Department of Medicine, College of Medicine, University of Ibadan, Nigeria
3 Dermatology Department, University Hospital Cheikh Khalifa and the University Hospital Mohammed VI. Faculty of Medicine, Mohammed VI University of Health Sciences (UM6SS), Casablanca, Morocco
4 Cairo Hospital for Dermatology & Venereology (Al-Haud Al-Marsoud), Cairo, Egypt
5 Gamal Abdel Nasser University, La Source University, Conakry, Guinea
6 Kilimanjaro Christian Medical University College (KCMUCo), Moshi, Tanzania
7 Regional Dermatology Training Centre (RDTC), Kilimanjaro Christian Medical Centre (KCMC) Hospital, Moshi, Tanzania

Key words: Dermoscopy, uses, dark skin, challenges

Citation: Enechukwu NA, Ogunbiyi AO, Kelati A, Sadek A, Traoré I, Mavura D. Dermoscopy Use in Africa: Determinants and Challenges. Dermatol Pract Concept. 2024;14(2):e2024098. DOI: https://doi.org/10.5826/dpc.1402a98

Accepted: December 20, 2023; Published: April 2024

Copyright: ©2024 Enechukwu et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Dr. Enechukwu Nkechi Anne, Senior Lecturer/ Honorary Consultant Dermatologist and Venereologist, Nnamdi Azikiwe University/ Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. E-mail: na.enechukwu@unizik.edu.ng

ABSTRACT

Introduction: Dermoscopy has evolved over the years beyond distinguishing benign pigmented lesions from melanoma to diagnosing virtually all diseases in dermatology. Overwhelming evidence demonstrates its utility in improving diagnostic accuracy, reducing unnecessary biopsies and lesion monitoring. Dermoscopy is widely used in Western nations, hence most descriptions of lesions in literature are predominantly on Fitzpatrick skin types I-III. Current evidence shows that there are unique dermoscopic features in the dark skin as a result of pigment and pathological reactions. Nationwide surveys and reports have been conducted across several continents to highlight prevalence and factors influencing dermoscopy use with the hope of maximizing its apparent benefits. There are currently no such reports from Africa.

Objectives: To evaluate dermoscopy use and its determinants among dermatologists in Africa.

Methods: A cross-sectional study. Online forms were e-mailed to individual practicing dermatologists and members of the African Society of Dermatologists and Venereologists.
Introduction

There has been a rising global recognition of the utility of dermoscopy for diagnosis and management of skin diseases beyond neoplastic lesions in all skin types [1-5]. In addition to improving diagnostic accuracy of skin lesions thereby facilitating triage of skin lesions in primary care dermatology while reducing unnecessary biopsies, it also improves precision in determining the margins of excision and monitoring of lesions during treatment [6-8].

Dermoscopy is widely used in Western nations, hence most dermoscopic description of skin lesions in literature are predominantly in Fitzpatrick skin types I-III [9-14]. Current evidence shows that certain dermoscopic features may be specific to skin of color as a result of the role of pigment and reactionary effects due to inflammation [15, 16]. Additionally, several skin diseases are exclusively seen or commoner in the darker skin types. There are several dermoscopic descriptions of a wide variety of skin diseases in the fairer skin which has been streamlined by the standardization of terminologies for diagnostic criteria for specific dermatoses [7, 17-19]. There are however relatively few studies on dermoscopic features of skin lesions in the darker skin phenotypes [15,16, 20]. Until recently, there has not been standardized terminologies for the dermoscopy of skin lesions in skin of color [21,22]. However, in order to demonstrate the diagnostic utility of dermoscopy and formulate useful diagnostic criteria in darker skin types, many more studies from this population are needed.

The degree of usefulness of dermoscopy and the precision of dermoscopic criteria is dependent on appropriate use which in turn depends on proper training, use of standardized guidelines and appropriate reporting [9]. There are several articles on the use of dermoscopy among dermatologists in Europe, Australia, U.K, USA and Saudi Arabia [5,9-11,23-31]. There are currently no reports on dermoscopy use in Africa although a greater majority of persons with darker skin phenotypes live in Africa. This survey was carried out to evaluate the use of dermoscopy among practicing dermatologists in Africa, determine factors that predict its use and the drawbacks (if any) to the use of dermoscopy in Africa. It will serve as a valuable groundwork for postulating why there are few reports from Africa and the findings can be used as a framework to enhance the use of dermoscopy in Africa.

Objectives

To evaluate the frequency of use of dermoscopy among African Dermatologists in their daily practice and to identify the determining factors, attitudes to use and also to highlight the obstacles to the use of dermoscopy among African dermatologists.

Methods

This was a cross sectional online survey conducted in Africa. Online forms were sent in person and through emails and/ or WhatsApp posts to dermatologists practicing in Africa and members of the African Society of Dermatologists and Venereologists over a 3-month period.

Study Participants

Participants were recruited from the African society of Dermatologists and Venereologists (ASDV) and Dermatologic societies in Africa. Members were emailed through the ASDV and the Nigerian Association of Dermatologists (NAD) mailing list and WhatsApp group page. Snowballing method was also used to share the link to the online survey (through colleague dermatologists) with other dermatologists practicing in Africa in their contact list. Respondents comprised specialist dermatologists (consultants) and dermatology residents. Public health practitioners and pediatricians who were affiliates of ASDV and NAD and also provide dermatologic care also participated. Reminders were sent fortnightly throughout the study period. Approval for the study was obtained from the Anambra State Ministry of Health Ethics Committee, Awka and informed consent was obtained from all study participants.

Study Instrument

The online questionnaire was semi structured and designed using guidelines in the technique and use of dermoscopy.

Results: There were 196 respondents from 24 African countries. Half of them used dermoscopy. Training, practice settings and location, provision of dermatoscopes by institutions and knowledge of criteria were notable significant determinants. Multiple training exposures, knowledge of criteria, availability of dermatoscopes, use of both hand-held and videodermatoscopes, average number of patients seen per day, and a positive outlook towards dermoscopy were significant determinants of frequency of use. Leading impediments were lack of training and inadequate dermatoscopes in practice.

Conclusions: Dermoscopy use in Africa is relatively low. Incorporating dermoscopy training into the curriculum with provision of dermatoscopes by training institutions will promote wider usage.
combined with other questions adapted from previous surveys on dermoscopy use [9,18, 19]. It had 31 multiple choice questions bordering on demographics, practice settings, dermoscopy training, availability of dermatoscopes, frequency of use, knowledge of indications for use, perceived diagnostic usefulness in skin of color; knowledge and use of techniques and dermoscopic criteria. It was originally designed in English language and was also translated to French.

Data Analysis
Data cleaning was done using Microsoft office Excel, version 2016 (Microsoft Corporation). Inadequate responses were removed from the data set. At the point of question on training, those without training were not allowed proceed with the rest of the survey, instead, they were directed to tell why they did not have training before submitting. All the respondents were classified as either user or non-users of dermoscopy. Users of dermoscopy were further classified into high frequency users (uses dermoscopy at least two times a week) and low frequency users (uses dermoscopy less than two times a week). Continuous variables (age, duration of practice and duration of training in dermoscopy) were summarized as mean and standard deviation; and then grouped into non-continuous variables. Non-continuous variables were summarized as frequency and percentages. Chi-square test for association (when expected cell count =>5) or Fisher’s exact test (when expected cell count <5) were used to check for associations between use of dermoscopy and sociodemographic and work variables; similarly, association between frequency of use and sociodemographic and work settings related variables were sought. Further analysis of interplay between the factors that influence use and frequency of use of dermoscopy was done using multinomial logistic regression statistics, employing the stepwise forward entry method. Predictors are given as adjusted odds ratios (AOR) with 95% confidence intervals (CI). In order to avoid over exaggerated odd ratios, categories of variables that were very few were removed from the models. A first model with several possible predictors was made; then, only the significant predictors from the first model were moved to a second model. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp.). For all inferential statistical methods, the threshold for statistical significance was predetermined at a significance level of p < 0.05.

Results
Socio-demographics
A total of 196 respondents (155 dermatology specialists, 29 senior residents, 11 junior residents and 1 intern) from 24 countries completed the survey with a response rate (proportion of respondents from the total number of dermatologists contacted through successfully delivered emails/posts) of 31.8% (Figure 1). A majority (72.4%) of the respondents were females with most practicing in public or government funded teaching Hospitals and in urban localities.

Determinants of Dermoscopy Use Among African Dermatologists
Half (50%) of the respondents used dermoscopy in their practice. The factors influencing the use of dermoscopy in practice settings included training in dermoscopy, country of practice, provision of dermatoscopes by training institutions and knowledge of dermoscopic criteria/guidelines for the diagnosis of skin diseases (Tables 1 and 2). Notably, only 32% of the respondent training centres provided dermatoscopes.

On multivariate analysis, practice settings and source of information about dermoscopy were significant predictors of use of dermoscopy. Public/government funded teaching hospitals (affiliated with universities) were more likely to use dermoscopy than public/government funded Federal Medical Centers (not affiliated with universities) with an odd ratio of 2.58 (P = 0.02). Those that heard about dermoscopy during residency training were more likely to use dermoscopy than those that heard it from conferences (odd ratio = 3.03 and P = 0.01); and from colleagues (odd ratio = 3.93 and P = 0.03). Put in a second model, practice setting was the only significant predictor with those in public/government funded teaching hospitals more likely to use dermoscopy than public/government funded federal medical centers, (odd ratio= 2.49; P = 0.02).

Frequency of Use of Dermoscopy
More than half (66.3%) of the individuals who used dermatoscopes were high frequency users (defined as using dermoscopy 2-3 times per week or every working day) while 33.7% were low frequency users (once in one or two weeks or rarely-less than once in two weeks). Provision of dermatoscopes by training centres (P = 0.02), average number of patients seen per day (P = 0.002), use of existing dermoscopic criteria to aid diagnosis of skin diseases (P = 0.009), a positive outlook towards dermoscopy with respect to dermatology practice (P = 0.007) and use of both hand-held and video dermatoscopes were significant determinants of frequency of use (Table 3).

On multivariate analysis, practice settings, current cadre, average number of patients seen daily, and number of training sessions were significant determinants of frequency of dermoscopy use. Those in Private Hospitals were less likely to be low frequency users than public/government funded teaching hospitals (odd ratio = 0.03, P = 0.02); Registrars/
residents were less likely to be low frequency users than specialists/consultants (odd ratio = 0.08, P = 0.05). Also, those that see <10 patients daily were more likely to be low frequency users than those seeing 21-50 patients (odd ratio = 41.53, P = 0.01), and those with <3 training were more likely to be low frequency users than those with =>3 training (odd ratio = 5.05, P= 0.05). All variables significant in the first model remained significant in the second model.

Impediments to the Use of Dermoscopy Among African Dermatologists

Half (50%) of the respondents reported not using dermoscopy. Notable setbacks to the use of dermoscopy were lack of training, technical/expertise support and challenges with interpretation of dermoscopic findings followed by unavailability of dermatoscopes (Figure 2).

A few of the respondents (5.6%) were not using dermoscopy in spite of having training. Reasons included: no access to a dermatoscopes (unable to buy personal ones) and lack of confidence in spite of training.

Dermoscopy Training

Some of the various training options by the respondents included hands on/on the job training, online/social media, conference, virtual, part of undergraduate/residency training and structured training (certification trainings). More than half of the respondents (52.6 %) had some form of training while 47.4% had no training at all. The most commonly

![Figure 1](image1.png)

**Figure 1:** (A) Distribution of respondents by country of practice. (B) Distribution of users by country (percentage users)
Table 1. Association between country of practice and use dermoscopy

<table>
<thead>
<tr>
<th>Country of practice</th>
<th>Non-users N (%)</th>
<th>Users N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigeria</td>
<td>39(50.6)</td>
<td>38(49.4)</td>
<td>77(100)</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>11(91.7)</td>
<td>1(8.3)</td>
<td>12(100)</td>
</tr>
<tr>
<td>Ghana</td>
<td>4(66.7)</td>
<td>2(33.3)</td>
<td>6(100)</td>
</tr>
<tr>
<td>South Africa</td>
<td>3(15)</td>
<td>17(85)</td>
<td>20(100)</td>
</tr>
<tr>
<td>Angola</td>
<td>1(50)</td>
<td>1(50)</td>
<td>2(100)</td>
</tr>
<tr>
<td>Tanzania</td>
<td>3(100)</td>
<td>0(0)</td>
<td>3(100)</td>
</tr>
<tr>
<td>Uganda</td>
<td>1(100)</td>
<td>0(0)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Kenya</td>
<td>2(100)</td>
<td>0(0)</td>
<td>2(100)</td>
</tr>
<tr>
<td>Malawi</td>
<td>0(0)</td>
<td>1(100)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Tunisia</td>
<td>0(0)</td>
<td>4(100)</td>
<td>4(100)</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1(100)</td>
<td>0(0)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1(100)</td>
<td>0(0)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Sudan</td>
<td>0(0)</td>
<td>1(100)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Senegal</td>
<td>5(83.3)</td>
<td>1(16.7)</td>
<td>6(100)</td>
</tr>
<tr>
<td>Madagascar</td>
<td>4(100)</td>
<td>0(0)</td>
<td>4(100)</td>
</tr>
<tr>
<td>Cameroun</td>
<td>2(100)</td>
<td>0(0)</td>
<td>2(100)</td>
</tr>
<tr>
<td>Guinea</td>
<td>1(100)</td>
<td>0(0)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Benin</td>
<td>2(100)</td>
<td>0(0)</td>
<td>2(100)</td>
</tr>
<tr>
<td>Ivory coast</td>
<td>2(100)</td>
<td>0(0)</td>
<td>2(100)</td>
</tr>
<tr>
<td>Mauritania</td>
<td>0(0)</td>
<td>1(100)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Egypt</td>
<td>7(28)</td>
<td>18(72)</td>
<td>25(100)</td>
</tr>
<tr>
<td>Maroc</td>
<td>7(35)</td>
<td>13(65)</td>
<td>20(100)</td>
</tr>
<tr>
<td>Gambia</td>
<td>1(100)</td>
<td>0(0)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Congo</td>
<td>1(100)</td>
<td>0(0)</td>
<td>1(100)</td>
</tr>
<tr>
<td>Total</td>
<td>98(50)</td>
<td>98(50)</td>
<td>196(100)</td>
</tr>
</tbody>
</table>

F(P value) 53.86(<0.01)

*a* indicates a strong likelihood that the country is either a user or non-user of dermoscopy depending on its specific placement.

reported mode of training was on the job training and hands-on training (Table 4). Reasons for not having dermoscopy training are highlighted in Figure 3. Determinants of training were country of practice (P < 0.001) and years of practice (P = 0.04). Interestingly, use and frequency of use of dermoscopy were significantly associated with the number of training activities undertaken (Table 5).

**Awareness and Use of Guidelines and Techniques in Dermoscopy**

A greater proportion (78.6%) of those who had training on dermoscopy were aware of the existence of dermoscopic criteria for skin diseases. While 55.3% use them always, 34% use them sometimes. Commonest reasons for use included ensuring uniformity of diagnosis and providing more confidence in diagnosis while the commonest reason for non-use was poor knowledge of and difficulty remembering different criteria.

**Indications for Use of Dermoscopy and Perceived Usefulness of Dermoscopy**

The common indications for the use of dermoscopy are mostly pigmented lesions and non-tumoral dermatoses as summarized in Figure 4. Majority (82.5%) of the respondents with training believed that the use of dermoscopy had improved their dermatologic practice, 10.7% did not think it improved their practice while 1.9% did not know if it did. Dermoscopy was considered most useful for diagnosis (91.6%), lesion monitoring (70.4%), treatment monitoring (61.4%), guidance for biopsy (60.2%) and considered least useful for patient education (1.2%) and hair transplantation (1.2%). On the perception on the usefulness of dermoscopy, majority of the respondents (84.5%) believed that dermoscopy was comparable to clinical examination with the unaided eye and histopathology while 1.9% and 8.7% thought clinical examination and histopathology were superior to dermoscopy respectively.
Table 2. Association between sociodemographic and other variables and use of dermoscopy

<table>
<thead>
<tr>
<th></th>
<th>Non-users</th>
<th>Users</th>
<th>Total</th>
<th>X(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Practice setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public /government funded</td>
<td>54(55.1)</td>
<td>63(64.3)</td>
<td>117(59.7)</td>
<td>6.28(0.09)</td>
</tr>
<tr>
<td>Teaching hospitals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federal Medical Centers</td>
<td>28(28.6)</td>
<td>14(14.3)</td>
<td>42(21.4)</td>
<td></td>
</tr>
<tr>
<td>Private hospital</td>
<td>11(11.2)</td>
<td>16(16.3)</td>
<td>27(13.8)</td>
<td></td>
</tr>
<tr>
<td>Private funded Teaching hospitals</td>
<td>5(5.1)</td>
<td>5(5.1)</td>
<td>10(5.1)</td>
<td></td>
</tr>
<tr>
<td>Place of practice</td>
<td></td>
<td></td>
<td></td>
<td>1.60(0.44)</td>
</tr>
<tr>
<td>Urban</td>
<td>78(79.6)</td>
<td>84(85.7)</td>
<td>162(82.7)</td>
<td></td>
</tr>
<tr>
<td>Semi-urban</td>
<td>16(16.3)</td>
<td>10(10.2)</td>
<td>26(13.3)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>4(4.1)</td>
<td>4(4.1)</td>
<td>8(4.1)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>1.63(0.21)</td>
</tr>
<tr>
<td>Male</td>
<td>31(31.6)</td>
<td>23(23.5)</td>
<td>54(27.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67(68.4)</td>
<td>75(76.5)</td>
<td>142(72.4)</td>
<td></td>
</tr>
<tr>
<td>Current Cadre</td>
<td></td>
<td></td>
<td></td>
<td>2.11(0.54)</td>
</tr>
<tr>
<td>Intern</td>
<td>1(1)</td>
<td>0(0)</td>
<td>1(0.5)</td>
<td></td>
</tr>
<tr>
<td>Registrar/Junior resident</td>
<td>5(5.1)</td>
<td>6(6.1)</td>
<td>11(5.6)</td>
<td></td>
</tr>
<tr>
<td>Senior Registrar/Senior Resident</td>
<td>17(17.3)</td>
<td>12(12.2)</td>
<td>29(14.8)</td>
<td></td>
</tr>
<tr>
<td>Specialist/Consultant</td>
<td>75(76.5)</td>
<td>80(81.6)</td>
<td>155(79.1)</td>
<td></td>
</tr>
<tr>
<td>Average number of patients seen in a day</td>
<td></td>
<td></td>
<td></td>
<td>1.44(0.69)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>18(18.4)</td>
<td>13(13.3)</td>
<td>31(15.8)</td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>55(56.1)</td>
<td>62(63.3)</td>
<td>117(59.7)</td>
<td></td>
</tr>
<tr>
<td>21-50</td>
<td>22(22.4)</td>
<td>21(21.4)</td>
<td>43(21.9)</td>
<td></td>
</tr>
<tr>
<td>51-100</td>
<td>3(3.1)</td>
<td>2(2)</td>
<td>5(2.6)</td>
<td></td>
</tr>
<tr>
<td>How did you hear about dermoscopy?</td>
<td></td>
<td></td>
<td></td>
<td>6.55(0.25)</td>
</tr>
<tr>
<td>No prior knowledge</td>
<td>3(3.1)</td>
<td>0(0)</td>
<td>3(1.5)</td>
<td></td>
</tr>
<tr>
<td>Residency training</td>
<td>51(52)</td>
<td>65(66.3)</td>
<td>116(59.2)</td>
<td></td>
</tr>
<tr>
<td>Conference</td>
<td>28(28.6)</td>
<td>22(22.4)</td>
<td>50(25.5)</td>
<td></td>
</tr>
<tr>
<td>Graduate certificate and MSc dermatology</td>
<td>2(2)</td>
<td>2(2)</td>
<td>4(2)</td>
<td></td>
</tr>
<tr>
<td>Colleagues</td>
<td>10(10.2)</td>
<td>6(6.1)</td>
<td>16(8.2)</td>
<td></td>
</tr>
<tr>
<td>Online</td>
<td>4(4.1)</td>
<td>3(3.1)</td>
<td>7(3.6)</td>
<td></td>
</tr>
<tr>
<td>Are you aware of guidelines or techniques to the use of dermoscopy in dermatology?</td>
<td></td>
<td></td>
<td></td>
<td>131.31(&lt;0.01)</td>
</tr>
<tr>
<td>Yes</td>
<td>1(1)</td>
<td>80(81.6)</td>
<td>81(41.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97(99)</td>
<td>18(18.4)</td>
<td>115(58.7)</td>
<td></td>
</tr>
<tr>
<td>Does your training center provide dermoscopes</td>
<td></td>
<td></td>
<td></td>
<td>39.68(&lt;0.01)</td>
</tr>
<tr>
<td>Yes</td>
<td>0(0)</td>
<td>33(33.7)</td>
<td>33(16.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>98(100)</td>
<td>65(66.3)</td>
<td>163(83.2)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

This is the first report evaluating the use of dermoscopy and its determinants among dermatologists in Africa. The low response rate was comparable with those recorded in most of the studies on dermoscopy in the literature [5,11, 27,30]. Various nationwide surveys and pan-continental studies from other continents reported dermoscopy use ranging from 56.9 % to 98% [5, 9-11,23-26,28-31]. Despite widespread awareness of its dermatological utility, dermoscopy use was predictably lower (50%) than in Western societies. This observation aligns with the evolving role of dermoscopy in diagnosing skin conditions in individuals with darker skin phototypes, a population largely represented in Africa [21,22,32,33]. Historically, dermoscopy had been used exclusively for distinguishing neoplastic lesions from pigmented and non-pigmented benign lesions in lighter skin phototypes [34]. These dermatoses were previously considered to be uncommon in skin of colour hence the erstwhile limitations to dermoscopy in the darker skin phototypes [21,22].

Secondly, dermatologic criteria for diagnosis of dermatosis in skin of colour have only recently been reported [21,22,22]. This may contribute to the limited use of dermoscopy in this region. Knowledge of dermatoscopic guidelines/criteria and techniques translates to confidence in
dermoscopic diagnosis and was found to be strongly associated with use in this study (Table 3) as was observed in some other studies [23,27]. Dermoscopy is now applicable across all skin types, including darker skin. Understanding its principles, methods, terminology, reporting, and criteria in diverse skin tones is crucial for its effective use, as highlighted by this study findings [21,22, 28, 30].

Undertaking training in dermoscopy, country of practice and certain practice settings (public/government funded teaching hospitals) significantly correlated with use in this study and was in consonance with findings from several studies [9, 11, 27, 29]. Lack of training as a major barrier to the use of dermoscopy among the respondents in our study was also consistently observed in several other studies [29,30 ,31,35]. There is compelling evidence from several studies that training is key in promoting the use of dermoscopy [9,10,26-28]. Dermoscopy training in Africa was low when compared to the Western societies some with training rates as high as 98% [9,11,12,25].

While training was generally less prevalent in many sub-Saharan African countries, our study revealed that countries with higher dermoscopy training rates (Egypt, South Africa, and Tunisia) may have well-structured dermoscopy training integrated into their curriculum or established as a standard practice in dermatology. This is evident in the significant association found between these countries and dermoscopy training. This emphasizes the low dermoscopy use, primarily due to limited training in these countries. Dermoscopy recent recognition in diagnosing darker skin explains this [21,22]. Integrating dermoscopy training in African curricula, along with raising awareness and offering diverse training opportunities, will enhance dermatologists skills.

### Table 3. Association between practice related factors and frequency of dermoscopy use

<table>
<thead>
<tr>
<th>Practice Related Factors</th>
<th>Low Frequency N (%)</th>
<th>High Frequency N (%)</th>
<th>OR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of patients seen in a day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>9(69.2)</td>
<td>4(30.8)</td>
<td>5.71(1.61-20.34)</td>
<td>0.01</td>
</tr>
<tr>
<td>10-20</td>
<td>22(35.5)</td>
<td>40(64.5)</td>
<td>0.75(0.29-1.91)</td>
<td>0.54</td>
</tr>
<tr>
<td>21-50</td>
<td>2(9.5)</td>
<td>19(90.5)</td>
<td>0.15(0.03-0.71)</td>
<td>0.01</td>
</tr>
<tr>
<td>51-100</td>
<td>0(0)</td>
<td>2(100)</td>
<td>0.37(0.01-8.12)</td>
<td>0.53</td>
</tr>
<tr>
<td>How did you hear about dermoscopy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residency training</td>
<td>27(41.5)</td>
<td>38(58.5)</td>
<td>3.19(1.16-8.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Conference</td>
<td>3(13.6)</td>
<td>19(86.4)</td>
<td>0.24(0.06-0.88)</td>
<td>0.03</td>
</tr>
<tr>
<td>Graduate certificate and MSc</td>
<td>1(50)</td>
<td>1(50)</td>
<td>2.00(0.12-33.02)</td>
<td>0.31</td>
</tr>
<tr>
<td>Colleagues</td>
<td>1(16.7)</td>
<td>5(83.3)</td>
<td>0.37(0.04-3.34)</td>
<td>0.22</td>
</tr>
<tr>
<td>Online</td>
<td>1(33.3)</td>
<td>2(66.7)</td>
<td>0.98(0.08-11.27)</td>
<td>0.98</td>
</tr>
<tr>
<td>Are you aware of guidelines or techniques to the use of dermoscopy in dermatology?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24(30)</td>
<td>56(70)</td>
<td>0.42(0.15-1.21)</td>
<td>0.11</td>
</tr>
<tr>
<td>No</td>
<td>9(50)</td>
<td>9(50)</td>
<td>2.33(0.82-6.60)</td>
<td>0.11</td>
</tr>
<tr>
<td>Does your training center provide dermoscopes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6(18.2)</td>
<td>27(81.8)</td>
<td>0.31(0.11-0.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>27(41.5)</td>
<td>38(58.5)</td>
<td>3.19(1.16-8.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Has the use of dermoscopy changed your management of dermatologic conditions in any way?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24(28.2)</td>
<td>61(71.8)</td>
<td>0.17(0.04-0.62)</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>7(63.6)</td>
<td>4(36.4)</td>
<td>4.10(1.11-15.23)</td>
<td>0.01</td>
</tr>
<tr>
<td>Don’t know</td>
<td>2(100)</td>
<td>0(0)</td>
<td>10.39(0.48-223.07)</td>
<td>0.12</td>
</tr>
<tr>
<td>Do you use existing dermoscopic criteria in the diagnosis of skin diseases?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14(24.6)</td>
<td>43(75.4)</td>
<td>0.37(0.15-0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>5(83.3)</td>
<td>1(16.7)</td>
<td>11.42(1.27-102.37)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sometimes</td>
<td>14(40)</td>
<td>21(60)</td>
<td>1.54(0.65-3.66)</td>
<td>0.32</td>
</tr>
<tr>
<td>What type of dermoscope do you use?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-held/Handyscope</td>
<td>28(37.3)</td>
<td>47(62.7)</td>
<td>2.14(0.71-6.41)</td>
<td>0.17</td>
</tr>
<tr>
<td>Videodermoscope</td>
<td>5(55.6)</td>
<td>4(44.4)</td>
<td>2.72(0.67-10.92)</td>
<td>0.15</td>
</tr>
<tr>
<td>Both</td>
<td>0(0)</td>
<td>12(100)</td>
<td>0.06(0.01-1.11)</td>
<td>0.05</td>
</tr>
<tr>
<td>Don’t know</td>
<td>0(0)</td>
<td>2(100)</td>
<td>0.37(0.01-8.12)</td>
<td>0.53</td>
</tr>
<tr>
<td>Are you aware of any complications from the use of dermoscopes?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11(44)</td>
<td>14(56)</td>
<td>1.82(0.71-4.63)</td>
<td>0.21</td>
</tr>
<tr>
<td>No</td>
<td>22(30.1)</td>
<td>51(69.9)</td>
<td>0.54(0.21-1.39)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.
The unavailability of dermatoscopes and the inability of training institutions to provide them posed significant challenges to dermoscopy use, contrary to findings in other studies where many respondents had access to dermatoscopes [5, 29]. In our study, the cost of dermatoscopes was also identified as a notable barrier, deviating from findings in other studies [9, 36]. Unfortunately, dermatoscopes are not locally produced in most sub-Saharan African countries, leading to high costs due to shipping and import duties. Interestingly, an Australian study revealed that despite respondents not owning personal dermatoscopes, practice centers supplied most of the devices used [36].

Dermatologists in academic Public/Government-funded Teaching Hospitals were more inclined to use dermoscopy compared to non-academic Public/Government-funded Federal Medical centers, which contrasts with findings in a French study [26]. This difference may be attributed to Teaching Hospitals involvement in dermatology research, academic programs, and residency training, which likely necessitate modern diagnostic methods like dermoscopy. Additionally, the availability of advanced medical equipment and referrals for complex cases requiring specialized diagnostic accuracy could drive the use of innovative diagnostic tools, including dermoscopy. Further studies are required to explore this observation.

In contrast to other studies that identified female gender, younger age, and years of experience as significant factors, our study did not find such associations [10, 23, 27, 30]. Nevertheless, our findings indicate that there are no gender or age constraints to dermoscopy use in our study population.

### Table 4. Association between type of training and use or non-use of dermoscopy use

<table>
<thead>
<tr>
<th>Kind of training received</th>
<th>Users versus non-users</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-users N (%)</td>
<td>Users N (%)</td>
<td>Total N (%)</td>
<td></td>
</tr>
<tr>
<td>On the job training</td>
<td>1(1.9)</td>
<td>52(98.1)</td>
<td>53(100)</td>
<td></td>
</tr>
<tr>
<td>Hands-on</td>
<td>0(0)</td>
<td>53(100)</td>
<td>53(100)</td>
<td></td>
</tr>
<tr>
<td>Virtual</td>
<td>0(0)</td>
<td>29(100)</td>
<td>29(100)</td>
<td></td>
</tr>
<tr>
<td>Part of undergraduate/postgraduate training</td>
<td>4(9.8)</td>
<td>37(90.2)</td>
<td>41(100)</td>
<td></td>
</tr>
<tr>
<td>Online/social media</td>
<td>0(0)</td>
<td>25(100)</td>
<td>25(100)</td>
<td></td>
</tr>
<tr>
<td>Graduate certificate and MSc</td>
<td>0(0)</td>
<td>12(100)</td>
<td>12(100)</td>
<td></td>
</tr>
<tr>
<td>Structured (certification) training</td>
<td>1(10)</td>
<td>9(90)</td>
<td>10(100)</td>
<td></td>
</tr>
<tr>
<td>Conference/workshops</td>
<td>0(0)</td>
<td>6(100)</td>
<td>6(100)</td>
<td></td>
</tr>
<tr>
<td>Chi-square(p-value)</td>
<td>13.79(0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
as was seen in one study, and further research is warranted to investigate the underlying reasons for this divergence [26].

Dermoscopy was more frequently utilized by respondents who had a higher patient load, had access to dermatoscopes, and held a positive view of dermoscopy diagnostic benefits while also adhering to diagnostic criteria. Dermatologists with a higher patient load are more likely to encounter diverse skin lesions, making dermoscopy a valuable diagnostic tool. Access to dermatoscopes and a positive view of its diagnostic utility, along with adhering to criteria, indicate a better understanding and promote its frequent use. This mirrors previous research, showing a consistent trend in dermoscopy utilization [9,35].

An intriguing discovery was the higher dermoscopy usage among residents compared to specialists/consultants, possibly due to younger individuals greater adoption of digital technology. Residents are also more inclined to use diagnostic aids, unlike experienced specialists.

We observed that there was an increased use of dermoscopy by those who were exposed to frequent training.
sessions which was not surprising as we felt that this translated to increasing confidence in the use of dermoscopy with more dermoscopy training exposures [26,27]. These findings also reiterate the key role of continuous standardized and structured training incorporating dermoscopic guidelines and criteria.

In contrast to several studies from other continents where dermoscopy is mainly used for distinguishing benign pigmented skin lesions from tumors, most of our respondents used dermoscopy for non-tumoral dermatoses (Figure 4) [23, 26, 31,36]. This is possibly due to the relatively lower incidence of skin tumors in darker skin types. Recent research, including our own, suggests an increasing trend in dermoscopy use for various conditions, like inflammatory and hair diseases, reflecting a growing awareness of dermoscopy utility in diagnosing non-tumoral skin diseases [5].

The underutilization of dermoscopy wide diagnostic potential, especially for vascular tumors, may be due to challenges visualizing blood vessels in darker skin due to pigment interference. This is exacerbated by the limited data and illustrations of dermoscopic characteristics in dark skin, as existing literature primarily focuses on features in lighter skin [15, 16,20].

This study limitations include potential responder bias from self-reported data in a voluntary online survey, possibly overestimating dermoscopy use and positive attitudes among specialists with specific interests or expertise in dermoscopy. Key factors such as training and familiarity with dermoscopic criteria may be more prevalent among participating dermatologists who actively seek knowledge and information about dermoscopy. To mitigate this bias, future research employing random sampling and diverse representation of dermatologists from varied backgrounds and practice settings in Africa.

Dermoscopy is an evolving practice in Africa although its use is currently low. Challenges to its use include unavailability of dermatoscopes and lack of training. Provision of dermatoscopes in practice settings/institutions, promoting opportunities for training in dermoscopy in the dark skin, inclusion of dermoscopy training in dermatology training curricula and having dedicated workshops will improve dermoscopy use in Africa.

Acknowledgements

The authors are grateful to Professor Manal Bosseila who assisted with sending online forms to colleagues in Egypt and Drs. Perpetua Ibekwe (ASDV) and Enzo Errichetti for assisting with reaching out to other colleagues in Africa.

References


Evaluation of the Quality of Life and the Demographic and Clinical Characteristics of Patients With Pemphigus With Oral Mucosal Involvement: A Multicenter Observational Study

Asude Kara Polat¹, Mehmet Kamil Mülayim², Tuğba Falay Gür³, Ayda Acar⁴, Burçin Cansu Bozca⁵, Can Ceylan⁶, Sadime Kılınç⁶, Rukiye Yasak Güner⁷, Hülya Albayrak⁸, Murat Durdu⁹, Ayşe Esra Koku Aksu¹⁰, Fatma Nalbant¹¹, Ekin Şavk¹², Dilek Bayramgürler¹³, Munise Daye¹⁴, Ralfi Singer¹⁵, Emine Tuğba Alataş¹⁶, Vefa Aslı Erdemir¹⁷, Mehmet Salih Gürel¹⁷, Soner Uzun⁵, Savaş Yaylı¹⁸

¹ Memorial Bahçelievler Hospital, Department of Dermatology, Istanbul, Turkey
² Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Dermatology, Kahramanmaraş, Turkey
³ University of Health Sciences, Sultan Abdullah Hamidi Training and Research Hospital, Department of Dermatology, Istanbul, Turkey
⁴ Ege University Faculty of Medicine, Department of Dermatology, Izmir, Turkey
⁵ Akdeniz University, Faculty of Medicine, Department of Dermatology, Antalya, Turkey
⁶ Ankara City Hospital, Department of Dermatology, Ankara, Turkey
⁷ Sivas Cumhuriyet University, Faculty of Medicine, Department of Dermatology, Sivas, Turkey
⁸ Namık Kemal University Faculty of Medicine, Department of Dermatology, Tekirdağ, Turkey
⁹ Başkent University Adana Dr. Turgut Noyan Application and Research Center, Department of Dermatology, Adana, Turkey
¹⁰ University of Health Sciences, İstanbul Training and Research Hospital, Department of Dermatology, İstanbul, Turkey
¹¹ Edirne Keşan State Hospital, Department of Dermatology, Edirne, Turkey
¹² Aydın Adnan Menderes University Faculty of Medicine, Department of Dermatology, Aydın, Turkey
¹³ Kocaeli University Faculty of Medicine, Department of Dermatology, Kocaeli, Turkey
¹⁴ Necmettin Erbakan University Meram Faculty of Medicine, Department of Dermatology, Konya, Turkey
¹⁵ Prof. Dr. Cemil Taşçoğlu City Hospital, Department of Dermatology, İstanbul, Turkey
¹⁶ Muğla Sıtkı Koçman University Faculty of Medicine, Faculty of Medicine, Department of Dermatology, Muğla, Turkey
¹⁷ Medeniyet University Faculty of Medicine, Department of Dermatology, İstanbul, Turkey
¹⁸ Koç University Faculty of Medicine, Department of Dermatology, İstanbul, Turkey

Key words: quality of life, oral health, oral mucosa, pemphigus


Accepted: November 11, 2023; Published: April 2024

Copyright: ©2024 Kara Polat et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Assoc. Prof. Asude Kara Polat, MD., Memorial Bahçelievler Hospital, Bahçelievler Merkez, Adnan Kahveci Blv. No: 227, 34180 Bahçelievler, İstanbul, Turkey. Phone number: +905052512142, Fax: +9002126320060, E-mail: asudekara@yahoo.com.tr
Introduction

Pemphigus vulgaris (PV) is an autoimmune disease characterized by intraepithelial bullae and erosions in the skin and mucosa [1]. The disease is characterized by painful erosions, irregularly circumscribed ulcers, and small vesicles and flaccid bullae, especially in the buccal mucosa and gingiva [2]. Yaylı et al in a 1-year prospective study that evaluated patients with pemphigus in Turkey found that the annual incidence of pemphigus was 4.7/1 million, and PV was determined as the most common clinical subtype (87.3%) [3]. The presence of painful lesions disrupt oral intake depending on their location and markedly impairs the quality of life for patients. In the existing literature, research on the quality of life in individuals with pemphigus is scarce, and it often evaluates pemphigus with other diseases within the pemphigus spectrum [4-7]. Only Ghodsi et al. have specifically evaluated the quality of life of patients with PV [7]. However, in this study a specialized scale designed specifically for patients with oral manifestations of PV was not used [7]. In Turkey, two studies have evaluated the quality of life of patients with autoimmune bullous diseases in general but no study has specifically evaluated the quality of life of patients with PV [8,9].

Objectives

This multicenter study aimed to determine the demographic, clinical and treatment characteristics of PV patients with oral mucosal involvement and to assess the impact on their quality of life.

Methods

We conducted a prospective observational study among 106 patients diagnosed with PV and presenting oral mucosal involvement. Demographic data, clinical and treatment characteristics, and quality of life questionnaires were recorded.

Results

The study included 106 patients, 55 (51.89%) were male and there was a predominance of the mucocutaneous subtype in 83 individuals (78.38%). Oral mucosa was the initial site of manifestation in 44 patients (41.51%). Bilateral buccal mucosa was the most frequently affected site. The predominant symptom reported was a burning sensation, noted in 91 patients (85.85%). Oral mucosal examination revealed erosions in 85.85% of the patients. Systemic steroids were the most commonly administered treatment, and rituximab was used in 18 patients (16.98%). A positive and significant correlation was found between pemphigus severity and Oral Health Impact Profile-14, Dermatology Life Quality Index and Dermatological Quality of Life Scale scores (P < 0.05). The presence of superficial ulcers, flaccid bullae, lesion diameter ≥1 cm, and >10 lesions were factors that markedly diminished quality of life. Complete response to treatment was noted in all patients administered rituximab.

Conclusions

The most common area of involvement was bilateral buccal mucosa, and the severity of PV closely correlated with a decline in quality of life measures. These results highlight the need for careful clinical oversight of PV, taking into account its effects on patients quality of life.
symptoms and findings in the oral mucosa), oral mucosal lesion type, number, diameter, disease severity, and disease activity and variables related to treatment and prognosis.

When assessing the severity of the disease, the Pemphigus Disease Severity Index (PDAI), a Pemphigus-Specific Severity Assessment scale developed in 2009 by Rosenbach et al, scored separately according to the number and diameter of lesions on the localized skin (12 anatomical regions), mucosal surface (12 anatomical regions), and scalp was used—230 points (120 points for the skin, 120 points for the mucosa, 10 points for the scalp) indicate disease activity and 13 points (12 points for the skin and 1 point for the scalp) indicate disease damage [11]. While evaluating the quality of life, the Oral Health Impact Profile-14 (OHIP14-TR) scale, Dermatology Life Quality Index (DLQI), and Dermatological Quality of Life Scale (DQLS) were used.

**Oral Health Impact Profile Scale**
The Oral Health Impact Profile (OHIP), which was first developed in Australia and consisted of 49 items, has been shortened due to its length, which made it time-consuming [12-14]. Basol et al, in 2014, developed and evaluated the Turkish OHIP14-TR, and its validity and reliability were demonstrated. The total scale score range is 0–56 [15].

**Dermatology Life Quality Index**
The DLQI scale, first created by Finlay and Khan in 1994, is an easy-to-use scale in practice and has been shown to be valid and reliable in Turkey [16,17].

**Dermatological Quality of Life Scale**
There are 11 questions in the DQLS developed by Gurel et al, and the total score range is 0–44 [18].

Statistical analyses were performed with the SPSS version 23.0 program. The conformity of the variables to the normal distribution was examined by histogram graphs and Kolmogorov-Smirnov/Shapiro-Wilk test. Mean, standard deviation, and median values were used when presenting descriptive analyses. The Mann–Whitney U test was used when evaluating non-normally distributed (nonparametric) variables between two groups, while the Kruskal–Wallis test was used when evaluating between more than two groups. The Bonferroni multiple comparison tests were used while investigating the reason for the significant difference between the groups. While presenting the categorical variables, the frequency and percentage values of the variables were used, and the analysis of the categorical variables was carried out with the chi-square (exact) test. The Spearman correlation test was used to evaluate the relationships between quantitative variables. Cases with a P value below 0.05 were considered statistically significant results.

**Results**
A total of 106 patients with PV with newly diagnosed oral mucosal involvement in 16 different dermatology clinics from different regions of Turkey were included in this study.

**Demographic and Clinical Characteristics of the Patients**
The mean age of all the patients was 50.06 ± 14.88 and 51.89% (N = 55) were males. While 34.91% were primary school graduates, 16.04% were university graduates. Body mass index was found to be 26.88 ± 4.04 (26.77). The most common personal disease history was diabetes (17.92%), followed by hypertension and coronary artery disease (Table 1). Of the patients, 19.81% were active smokers and 9.43% were regular alcohol users. Among the autoimmune diseases, Hashimoto thyroditis was found in four patients, rheumatoid arthritis in two, Sjögren syndrome in one, and Graves in one.

**Clinical Features of Pemphigus Disease**
The mean age of pemphigus onset was 49.45 ± 14.98 years, the mean duration of illness was 7.59 ± 8.57 months, and the mean delay in diagnosis was 4.39 ± 5.26 months. There was no family history of pemphigus in 99.06% of the patients.

Mucocutaneous subtype was found in 78.38% of the patients. While the initial localization of 41.51% of the patients was only the oral mucosa, 7.55% had only the skin, 40.57% had the oral mucosa and skin simultaneously, and 7.55% had the first lesions on the skin. The body surface area involved was localized in 50.94% of the patients.

The involvement of the oral mucosa with PV in 63.21% of the patients was in the bilateral buccal mucosa, followed by the lower lip (46.23%) and the tongue (45.28%). In 98.11% of the patients, symptoms were present in the oral mucosa and most commonly (85.83%) accompanied by burning; 77.36% had pain and 0.94% had difficulty swallowing. Oral mucosal examination revealed erosions in 85.85% of the patients, superficial ulcers in the oral mucosa in 66.04%, small vesicles in 12.26%, and flaccid bullae in 10.38%. Of the patients, 57.55% had lesion(s) 1 cm or more in diameter. While the mean PDAI was 27.58 ± 21.28, the mean damage score was 0.89 ± 3.01 (Table 1). The mean PDAI mucosal score, which indicates the severity of the disease, was 15.19 ± 13.68 and the PDAI oral mucosa mean score was 13.85 ± 12.17.

**Treatment Features**
Systemic steroids were the most commonly administered treatment (N = 88, 83.02%). This was followed by topical steroid (N = 42, 39.62%) and rituximab (RTX) (N = 18, 16.98%) treatments. Other agents used in the treatment
Table 1. Sociodemographic characteristics and disease-related features of the patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD or N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, x ± s.s. (median) (year)</td>
<td>50.06 ± 14.88 (52.00)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51 (48.11)</td>
</tr>
<tr>
<td>Male</td>
<td>55 (51.89)</td>
</tr>
<tr>
<td>Body mass index (x ± s.s. (median))</td>
<td>26.88 ± 4.04 (26.77)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (16.04)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (17.92)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4 (3.77)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>6 (5.66)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (11.32)</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>2 (1.89)</td>
</tr>
<tr>
<td>Others (neurological, rheumatological, chronic obstructive pulmonary diseases)</td>
<td>6 (5.66)</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>7.59 ± 8.57 (4.00)</td>
</tr>
<tr>
<td>Delay in diagnosis (months)</td>
<td>4.39 ± 5.26 (3.00)</td>
</tr>
<tr>
<td>Age-onset of pemphigus x ± s.s. (median)</td>
<td>49.45 ± 14.98 (51.00)</td>
</tr>
<tr>
<td>Family history of pemphigus</td>
<td>1 (0.94)</td>
</tr>
<tr>
<td>Retained body surface area</td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>57 (53.77)</td>
</tr>
<tr>
<td>Generalized</td>
<td>49 (46.23)</td>
</tr>
<tr>
<td>Clinical subtype</td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>83 (78.30)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>23 (21.70)</td>
</tr>
<tr>
<td>Onset location</td>
<td></td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>44 (41.51)</td>
</tr>
<tr>
<td>Skin</td>
<td>8 (7.55)</td>
</tr>
<tr>
<td>Oral mucosa and skin (both)</td>
<td>43 (40.57)</td>
</tr>
<tr>
<td>Scalp</td>
<td>1 (0.94)</td>
</tr>
<tr>
<td>Nasal mucosa</td>
<td>2 (1.89)</td>
</tr>
<tr>
<td>Oral mucosa &amp; skin &amp; scalp</td>
<td>2 (1.89)</td>
</tr>
<tr>
<td>Oral nasal anogenital</td>
<td>5 (4.72)</td>
</tr>
<tr>
<td>Oral nasal skin</td>
<td>1 (0.94)</td>
</tr>
<tr>
<td>Involvement site in the oral mucosa</td>
<td></td>
</tr>
<tr>
<td>Bilateral buccal mucosa</td>
<td>67 (63.21)</td>
</tr>
<tr>
<td>Hard palate</td>
<td>50 (47.17)</td>
</tr>
<tr>
<td>Lower lip</td>
<td>49 (46.23)</td>
</tr>
<tr>
<td>Tongue</td>
<td>48 (45.28)</td>
</tr>
<tr>
<td>Gingiva</td>
<td>43 (40.57)</td>
</tr>
<tr>
<td>Soft palate</td>
<td>40 (37.74)</td>
</tr>
<tr>
<td>Upper lip</td>
<td>33 (31.13)</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>29 (27.36)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>22 (20.75)</td>
</tr>
<tr>
<td>Unilateral buccal mucosa</td>
<td>18 (16.98)</td>
</tr>
<tr>
<td>Symptom in the oral mucosa</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>104 (98.11)</td>
</tr>
<tr>
<td>Pain</td>
<td>91 (85.85)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>82 (77.36)</td>
</tr>
<tr>
<td>Clinical findings in the oral mucosa</td>
<td></td>
</tr>
<tr>
<td>Erosions</td>
<td>91 (85.85)</td>
</tr>
<tr>
<td>Superficial ulcer</td>
<td>70 (66.04)</td>
</tr>
<tr>
<td>Small vesicles</td>
<td>13 (12.26)</td>
</tr>
<tr>
<td>Flaccid bullae</td>
<td>11 (10.38)</td>
</tr>
</tbody>
</table>
21.37 ± 11.30, respectively) were statistically significantly higher than those with only mucosal involvement (P < 0.001 and P = 0.010, respectively). No statistically significant difference was observed between the mean scores of OHIP14-TR (27.70 ± 13.53 and 24.57 ± 11.96, respectively) in the disease progressing with involvement (P = 0.351) (Table 4).

Conclusions
PV is an autoimmune disease characterized by the development of autoantibodies against intracellular adhesion proteins in the epidermis and progresses with intraepidermal bullae and erosions in the skin and mucous membranes [1]. Oral mucosal involvement is quite high in the disease [19-21], and has been reported as the most common initial localization in previous studies globally [22,23-25]. In our study, the most prevalent initial presentation was oral mucosal involvement, occurring in 41.51% of the patients, which is consistent with the literature. It is also noted that pemphigus vulgaris may manifest with concurrent cutaneous and oral mucosal involvement which was observed in 40.57% of our study participants [23-25]. Additionally, the onset of the disease can occur in other mucosal areas including nasal, anogenital, conjunctival, as well as the laryngeal and pharyngeal regions. Notably, in our study, nasal mucosal presentation was the initial sign in two individuals. Oral mucosal involvement typically manifests with symptoms such as pain, a burning sensation, and challenges in eating, were azathioprine (N = 16, 15.09%), intravenous immunoglobulin (IVIG) (N = 5, 4.72%), and mycophenolate mofetil (N = 5, 4.72%). Of the patients, 78.3% received inpatient treatment.

Evaluation of Quality of Life Scales
The mean DLQI of the patients was 11.6 ± 9.01, the DQLS mean 19.98 ± 11.34, and the OHIP14-TR mean was 27.02 ± 13.21. A positive and significant correlation was found between pemphigus severity and OHIP14-TR, DLQI, and DQLS scores (P < 0.05). There was a positive and significant relationship between PDAI mucosa and OHIP14-TR and DLQI, as well as between PDAI oral mucosa and OHIP14-TR. While there was a moderately strong relationship between PDAI and DLQI, other significant relationships were of low strength (Table 2).

OCHIP14-TR and DLQI scores were significantly higher in patients with superficial ulcers in the oral mucosa than those without, and this was statistically significant (P < 0.05). OHIP14-TR and DQLS scores were significantly higher in patients with flaccid bullae in the oral mucosa than those without and were statistically significant (P < 0.05). Those with more than 10 lesions in the oral mucosa had a significantly higher DQLS score. Again, the OHIP14-TR score was found to be significantly higher in patients with a lesion diameter of 1 cm and above in the oral mucosa (Table 3).

In the disease progressing with mucocutaneous involvement, the mean scores of DLQI and DQLS (13.24 ± 9.06 and 21.37 ± 11.30, respectively) were statistically significantly higher than those with only mucosal involvement (P < 0.001 and P = 0.010, respectively). No statistically significant difference was observed between the mean scores of OHIP14-TR (27.70 ± 13.53 and 24.57 ± 11.96, respectively) in the disease progressing with involvement (P = 0.351) (Table 4).

Table 2. The relationship between pemphigus severity and quality of life scale scores.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OHIP-14-TR</th>
<th>DLQI</th>
<th>DQLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.193</td>
<td>0.494</td>
<td>0.232</td>
</tr>
<tr>
<td>P</td>
<td>0.047</td>
<td>&lt; 0.000</td>
<td>0.017</td>
</tr>
<tr>
<td>PDAI mucosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.207</td>
<td>0.208</td>
<td>0.016</td>
</tr>
<tr>
<td>P</td>
<td>0.033</td>
<td>0.032</td>
<td>0.870</td>
</tr>
<tr>
<td>PDAI oral mucosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.194</td>
<td>0.184</td>
<td>0.016</td>
</tr>
<tr>
<td>P</td>
<td>0.046</td>
<td>0.059</td>
<td>0.869</td>
</tr>
</tbody>
</table>

DLQI = Dermatology Life Quality Index; DQLS = Dermatological Quality of Life Scale; OHIP-14-TR: Oral Health Impact Profile-14-TR scale; PDAI = Pemphigus disease area index.

PDAI = Pemphigus disease area index.
significantly impairing the patients quality of life. We found that OHIP-14-TR was significantly affected in patients with superficial ulcers, loose bullae, and lesion diameter of 1 cm and above in the oral mucosa compared to those without. Again, the DYSQS score was found to be significantly higher in patients with more than 10 lesions in the oral mucosa.

Godshi et al found burning sensations in 83.1% of patients and pain in 68.4% [7]. This is consistent with our findings in which the most common symptom was burning (n = 91, 85.85%), followed by pain (N = 82, 77.36%), while one patient had swallowing difficulties.

In the literature, several studies from various countries have evaluated the quality of life of patients with autoimmune bullous diseases. The number of patients with PV in these studies ranged from 32 to 43 [4-6]. Only Ghodsi et al have evaluated the quality of life in a study involving 61 patients with a diagnosis of PV [7]. In this context, various scales were used [9,11,26], as there are different quality-of-life scales for diseases with oral mucosal involvement [13,27,28]. In Godshi et al study, the most common clinical subtype was mucocutaneous (72%), followed by mucosal (20%) subtype. Similarly, the most frequently observed subtype in our study was mucocutaneous [7].

Oral mucosal lesions can be observed as painful erosions, irregularly circumscribed ulcers, small vesicles, and loose bullae and bulla residues anywhere in the oral mucosa, often in the buccal mucosa and gingiva [29]. Uzun et al reported that the disease started with persistent oral ulcers and erosion in 101 patients with PV [22]. In our study, 85.85% of the patients had erosions, 66.04% had superficial ulcers in the oral mucosa, 12.26% had small vesicles, and 10.38% had loose bullae. Suliman et al study, the most common site of involvement was found to be the buccal mucosa [2]. In our study, the most common site of oral involvement was the bilateral buccal mucosa with a rate of 63.21%. The severity of oral involvement is variable. Lesions may be localized or widespread. Symptoms may differ depending on the area of involvement and the number of lesions and their diameter, and the impact on quality of life may differ. The lesion diameter was 1 cm and above in 57.55% of the patients.
PV is observed more frequently in individuals aged 40–60 years. In the study conducted by Thansov et al over a 16-year period, the onset of the disease was observed in the 5th or 6th decade of life. Bozdag et al reported the mean age of onset of the disease as 48.3 ± 12.6 years [30,31]. In our study, similar to the literature, the median age at onset was 49.45 ± 14.98 (51.00) years. Pemphigus is observed more frequently in women according to most of the literature [7,23,31]. In a retrospective study by Abdolsamadi et al in which they examined 20 years of data on patients with pemphigus in Tehran, 380 (56.9%) patients with PV with only oral mucosal involvement were females, while 288 (43.1%) were males [32]. In the same study, 146 (62.9%) of 232 patients with oral mucosa and skin involvement were females and 86 (37.1%) were males [32]. In the study conducted by Arduino et al with patients with OPV in Italy, 62.25% of the patients were females [20]. In contrast to the literature, most of the patients in our study were males (n = 55, 51.89%).

The association of pemphigus with various autoimmune diseases has been reported in the literature. In Taiwan, Chiu et al examined the co-existing autoimmune diseases in patients with pemphigus and observed that pemphigus was most commonly accompanied by Sjögren syndrome, psoriasis, systemic lupus erythematosus, and alopecia areata. [33] In our study, Sjögren syndrome accompanied PV in one patient, while four patients had Hashimoto thyroiditis, one had Graves, rheumatoid arthritis, and two had rheumatoid arthritis. Chiu et al found no statistically significant relationship between pemphigus and other diseases such as Graves disease, Hashimoto thyroiditis, pernicious anemia, rheumatoid arthritis, vitiligo, or ankylosing spondylitis [33].

Regarding treatment, systemic steroids, azathioprine, mycophenolate mofetil, methotrexate, chlorambucil, cyclophosphamide, cyclosporine, rituximab, and IVIG can be used for patients with PV. Again, intralesional corticosteroid injections, Orobase or inhaled steroids, and antiseptic mouthwashes are used to treat oral mucosal lesions [34]. In our study, 88 (83.02%) patients with pemphigus vulgaris used IVIG. Fortuna et al used RTX as a combination therapy or alone in the treatment of 10 patients with OPV and reported a successful response in all the patients [35]. We treated 18 patients with OPV in our study with RTX and obtained a successful response in all of them.

In our study, we determined the sociodemographic, clinical and treatment, and quality of life characteristics of PV disease with oral mucosal involvement were determined. The most common area of involvement was bilateral buccal mucosa, and the quality of life was affected in correlation with the severity of the disease. Notably, a marked decline in quality of life was noted among patients presenting with superficial ulcers, flaccid bullae, lesions measuring 1 cm or more in diameter, and those with more than ten lesions within the oral cavity. A successful response was observed in all the patients that used RTX as a treatment agent.

References


29. Baykal C. Dermatoloji Atlası. İstanbul: Nobel Tip Kitabevi; 2012. PLEASE PROVIDE PAGES


34. Bologna JL, Schaffer JV, Duncan KO, Ko C. Dermatology Essentials. Elsevier Saunders; 2014. PLEASE PROVIDE PAGES

Efficacy of Low-Level Laser Versus Topical Erythromycin 2% in the Treatment of Inflammatory Acne Vulgaris

Samar Saeed Ashmawy, Elham Mohamed Kassem, Shereen Farouk Gheida, Nahla Elsayed Ramzy

Dermatology and Venereology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Key words: low-level laser, acne vulgaris, topical erythromycin

Citation: Saeed Ashmawy S, Mohamed Kassem E, Farouk Gheida S, Elsayed Ramzy N. Efficacy of Low-Level Laser Versus Topical Erythromycin 2% in the Treatment of Inflammatory Acne Vulgaris. Dermatol Pract Concept. 2024;14(2):e2024048. DOI: https://doi.org/10.5826/dpc.1402a48

Accepted: October 30, 2023; Published: April 2024

Copyright: ©2024 Saeed Ashmawy et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Samar Saeed Ashmawy, Dermatology and Venereology Department, Faculty of Medicine, Tanta University, Tanta, Egypt. Telephone: 01027905166 Email: samarashmawy88@gmail.com

ABSTRACT

Introduction: Acne vulgaris is a skin problem affecting many people of different ages. Despite many options that are available for treatment of acne vulgaris, many patients still respond inadequately to treatment. Phototherapy is one of the best acne treatment options.

Objectives: It was to compare the efficacy of low-level laser therapy in treatment of inflammatory acne versus topical erythromycin 2% cream.

Methods: This study included 40 patients (18 males, 22 females) with different clinical severities of acne vulgaris. All the participants underwent split-face treatment: one side with 8 treatments (twice per week) of a low-level continuous infrared diode laser (808 nm) wavelength and (500 Hz) frequency and the other side with topical erythromycin 2% twice daily (aknemycin cream 2%). Evaluation was done at start of sessions, 2 weeks after the end of sessions and 3 months after stoppage of treatment depending on: photographs, global evaluation of acne scale, and Indian acne association grading.

Results: There was improvement of acne lesions on laser side and antibiotic side (assessed as non-inflammatory and inflammatory lesion counts). Laser side showed better results than antibiotic side. Patients were more satisfied with laser treatment due to minimal side effects and less relapse.

Conclusions: A series of 8 treatments using low level continuous infrared diode laser represents a cheap, safe and effective non-invasive therapeutic option for acne vulgaris.
Introduction

Acne vulgaris (AV) is a common disease of the pilosebaceous unit (PSU) of the skin and may be either non-inflammatory (open and closed comedones) or inflammatory (papules and pustules) [1]. Traditional treatments for AV include topical medications such as antibiotics, retinoids, benzoyl peroxide (BPO), alpha hydroxyl acids (AHA), salicylic acid (SA), or azelaic acid (AA). In severe cases, systemic antibiotics such as tetracycline and doxycycline, oral retinoids, and some hormones are indicated. Despite many options available for treatment of AV, many patients still respond inadequately to treatment [2]. Phototherapy (light, lasers and photodynamic therapy (PDT)) has been proposed as an alternative therapeutic modality to treat AV with fewer side effects compared to other treatment options [3]. Low-level laser therapy (LLLT) is a fast-growing technology used to treat conditions that require stimulation of healing, relief of pain and inflammation, and restoration of function [4]. This approach has also been used for inflammatory acne by decreasing expression of cyclooxygenase 2 (cox-2) enzyme leading to inhibition of production of pro-inflammatory cytokines like tumor necrosis-alpha (TNF-α) and interleukin 1alpha (IL-1α) and so reduce inflammation [5,6]. The LLLT involves exposing cells to low levels of red and near infrared (NIR) light which is called ‘low-level’ because the energy or power densities employed are low compared to other forms of laser [7].

Objectives

It was to compare the efficacy of low-level laser therapy in treatment of inflammatory acne versus topical erythromycin 2% cream.

Methods

This study was right-left comparative study on 40 patients with inflammatory AV. They were selected from the Outpatient Clinic of Dermatology and Venereology Department, Faculty of Medicine, Tanta University Hospitals.

Inclusion Criteria

1. Patients suffering from inflammatory AV.
2. Patients who did not receive systemic or topical treatment 6 weeks before enrollment in the study.

Exclusion Criteria

Pregnancy, breast feeding, subjects with dermatological diseases other than acne, chronic diseases such as chronic liver and renal diseases, autoimmune diseases, photosensitive patients and patients using photo-sensitive drugs, cancer, pacemaker, epileptic seizures.

Study Assessments

All patients were subjected to history taking, examination, evaluation by:

1. The GEA (Global Acne Severity) Scale: based on photographic and clinical assessment of acne patients (Table 1). This assessment was done before starting therapy, at the end of 8 sessions of the therapy (after 1 month) and 3 months after stoppage of any treatment.
2. The Indian Acne Association (IAA) grading: based on type and number of acne lesions (Table 2).

Every patient received an explanation of nature, risks and purpose of the study, an informed consent was obtained, digital photographs were taken before starting therapy and at every visit till the end of the therapy and 3 months after that.

Therapeutic Regimen

1. In this study 40 patients with inflammatory acne were subjected to be treated by LLL (ENDOLASER 422. Enraf-nonius B. V, Netherlands). It is a low level continuous IR diode laser (808nm) wave length and (500HZ) frequency with a peak power of 500mW. The laser probe is 500 Mw continuous laser diode (LP500) with peak power of 500 W.

<table>
<thead>
<tr>
<th>Table 1. Global evaluation of acne scale.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>V</td>
</tr>
</tbody>
</table>
2. The patients were treated as split face (one side treated with topical erythromycin 2% twice daily and the other side with LLL device) in Physical Medicine Department, Faculty of Medicine, Tanta University Educational Hospital.

3. Number of sessions was 2 per week for 4 weeks.

4. Methods of application of cold laser: Patient was seated in a comfort position and wore protective glasses (Endolaser 422). The probe was in contact with the treated area by multiple applications of cold laser in multiple points. The probe was applied for 5 minutes per point of the affected area with the dose of 1.5 J/cm².

5. The patients were advised not to use any other treatment for acne during laser therapy and 3 months after last session.

6. Side effects were reported by the patients.

Assessment of the Efficacy of the Therapeutic Procedure

1. Photographs: They were taken at baseline and before each session then after 3 months of last session for follow up. Photos were taken by Samsung ST150F smart compact camera, 5x telephoto, F2.5 lens, and 16.2 MP resolution.

2. The GEA scale: of the inflammatory acne lesions before starting treatment, 2 weeks after the last session and three months later.

3. The IAA grading: according to number and type of the lesions.

4. Three blinded dermatologists: were asked to record percentage of improvement for each patient after completion of the treatment by comparing digital photographs before starting treatment and 2 weeks after the last session according to quartile grading scale: No improvement: if improvement was 0%, fair improvement: 0-25%, moderate improvement: 26-50%, marked improvement: 51-75%, excellent improvement: 76-100%.

5. Patient satisfaction: whether the patient was unsatisfied, slightly satisfied, satisfied or very satisfied.

Follow-up

Follow up of the patients after end of treatment sessions monthly for 3 months to observe efficacy, recurrence or side effects.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and inter-quartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were Chi-square test, McNemar and marginal homogeneity test, Wilcoxon signed ranks test, Kruskal Wallis test and F-test (ANOVA).

P value was considered statistically significant at $P \leq 0.05$, and statistically high significant at $P < 0.001$.

Results

Clinical results were demonstrated in Table 3. Comparison between laser and antibiotic side (Table 4). Comparison between two sides according to type of lesions (Table 5). Degree of improvement (Table 6). There was no statistically significant difference between both sides except in relapse where

<table>
<thead>
<tr>
<th>Grades</th>
<th>Comedones</th>
<th>Papules/Pustules</th>
<th>Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&lt;30</td>
<td>&lt;10</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>Any number</td>
<td>&gt;10</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Severe</td>
<td>Any number</td>
<td>Any number</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

Table 2. Indian acne association grading of acne severity.

Table 3. Demographic data of the studied cases (N = 40).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>45.0</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>55.0</td>
</tr>
<tr>
<td>Age Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.25 ± 1.65</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>19.0 (18.0 – 21.0)</td>
<td></td>
</tr>
<tr>
<td>Duration (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max</td>
<td>0.50 – 7.0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.53 ± 1.77</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.50 (2.0 – 5.0)</td>
<td></td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>55.0</td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>45.0</td>
</tr>
<tr>
<td>Aggravating factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>15.0</td>
</tr>
<tr>
<td>Sun exposure</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Sun exposure, food</td>
<td>4</td>
<td>10.0</td>
</tr>
<tr>
<td>Food</td>
<td>10</td>
<td>25.0</td>
</tr>
<tr>
<td>Menses</td>
<td>10</td>
<td>25.0</td>
</tr>
<tr>
<td>Sun exposure, menses</td>
<td>6</td>
<td>15.0</td>
</tr>
<tr>
<td>Sun exposure, menses, food</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Laser side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>12</td>
<td>30.0</td>
</tr>
<tr>
<td>Left</td>
<td>28</td>
<td>70.0</td>
</tr>
<tr>
<td>Type of lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papulopustular</td>
<td>30</td>
<td>75.0</td>
</tr>
<tr>
<td>Nodulocystic</td>
<td>10</td>
<td>25.0</td>
</tr>
</tbody>
</table>

IQR = Inter quartile range; SD = Standard deviation.
laser side showed less relapse than antibiotic side (Table 7). Evaluation of follow up after 3 months of both modalities of treatment according to the GEA scale (Table 7). Figures 1-3 show the change occurs from the start of the treatment to three months after the treatment and also comparing the antibiotic and laser sides in three cases.

**Conclusions**

In the current study, there was improvement in acne after treatment according to the GEA scale. By comparing both sides, laser side was better in treatment of AV than antibiotic side.

Our results were supported by study of Szymańska et al as they showed that treatment of acne with a LLLT for 10 minutes by a device with a power of 360 mW emits IR radiation with a wavelength of 785 nm and a power density of 80 mW/cm² showed significant improvement in acne lesions and decrease in skin sebum excretion was observed after the treatment with no adverse effects [9].

Other studies proposed that blue and red light may act synergistically in improving acne by combining anti-bacterial...
and anti-inflammatory action, rendering phototherapy with blue (415 nm) ± red (660 nm) light an effective and safe treatment for AV [10-12].

Aziz-Jalali MH, et al. showed that LLLT using 630-nm laser (red spectrum) significantly reduces active acne lesions after 12 sessions of treatment. They concluded that LLLT in red spectrum is a safe modality in treating facial AV without any complication [3].

There were no previous studies comparing split face treatment one side with LLLT alone and the other side with topical antibiotic alone. It is possible to use LLLT in combination with pharmacological treatment. There was one study demonstrating significant reduction in active acne lesions after 12 sessions using 630-nm red LLLT with a fluence of 12 J/cm² twice a week for 12 sessions with 2% topical clindamycin [13]. A few studies also showed that the combination of blue and red light have synergistic effects in acne treatment [14].

In the current study, there was statistically significant improvement of papulopustular, nodulocystic and associated comedonal lesions on laser side. The papulopustular lesions showed a statistically highly significant value.

Szymańska A, et al. showed significant improvement in non-inflammatory and inflammatory lesion counts with no adverse effects reported with a LLL [15]. It is also worth mentioning that in most studies improvement in inflammatory lesions was higher than the improvement in comedones. The analysis of the effectiveness of the performed procedures was based on sebumetric examination, photographs and the change in the number of acne lesions [9].

Another study has also shown a positive interaction between light, specifically red, and the release of anti-inflammatory cytokines, which is one of the mechanisms in the pathogenesis of acne [16].

A well-controlled single-blind study compared mixed blue (415 nm) and red light (660 nm) with blue light alone. They were compared with cool white light and 5% BPO. The patients were with mild and mild/moderate acne. There was a significant difference between the white light group and other therapies; the combined blue-red light was generally better than blue light alone. The data for comedone counts

<table>
<thead>
<tr>
<th>Degree of Improvement</th>
<th>Laser side (N = 40)</th>
<th>Antibiotic side (N = 40)</th>
<th>MH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>2</td>
<td>6</td>
<td>15.0</td>
<td>16.50</td>
</tr>
<tr>
<td>Fair</td>
<td>4</td>
<td>6</td>
<td>15.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>6</td>
<td>15.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Marked</td>
<td>2</td>
<td>6</td>
<td>15.0</td>
<td>22.5</td>
</tr>
<tr>
<td>Excellent</td>
<td>30</td>
<td>22</td>
<td>55.0</td>
<td>55.0</td>
</tr>
</tbody>
</table>

MH = Marginal Homogeneity Test.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Laser side (N = 40)</th>
<th>Antibiotic side (N = 40)</th>
<th>χ²</th>
<th>McNp</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>12</td>
<td>6</td>
<td>1.290</td>
<td>0.375</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>34</td>
<td>0.728</td>
<td>0.375</td>
</tr>
<tr>
<td>Transient erythema</td>
<td>8</td>
<td>4</td>
<td>0.784</td>
<td>0.625</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>14</td>
<td>8</td>
<td>1.129</td>
<td>0.375</td>
</tr>
<tr>
<td>Erythema and relapse</td>
<td>2</td>
<td>10</td>
<td>3.137</td>
<td>0.125</td>
</tr>
<tr>
<td>Relapse</td>
<td>0</td>
<td>12</td>
<td>7.059</td>
<td>0.031</td>
</tr>
<tr>
<td>Pigmentation and relapse</td>
<td>4</td>
<td>0</td>
<td>2.105</td>
<td>0.500</td>
</tr>
<tr>
<td>GEA I</td>
<td>34</td>
<td>18</td>
<td>6.50*</td>
<td>0.020</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>18</td>
<td>4.50</td>
<td>0.020</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>2</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAA No</td>
<td>34</td>
<td>18</td>
<td>6.50*</td>
<td>0.020</td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>18</td>
<td>4.50</td>
<td>0.020</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>4</td>
<td>10.0</td>
<td></td>
</tr>
</tbody>
</table>

IAA = Indian Acne Association; GEA = Global Acne Severity; McN = McNemar test.
monotherapy with topical antibiotics in the management of acne is not recommended. The main topical antibiotics are clindamycin and erythromycin [18].

Ross JI, et al. showed that the widespread use of topical erythromycin and clindamycin to treat acne has resulted in dissemination of cross-resistant strains of propionibacteria [19]. As bacterial antibiotic resistance continues to emerge as a serious global threat, it is crucial that all clinicians re-examine their use of antibiotics. The idea of “no more antibiotics for acne” should at least provoke thoughtful self-appraisal of current prescribing habits for many others [20].

Another study included 96 patients with mild to moderate AV who were treated with 2% alcoholic solution of showed a significant reduction occurred with active therapy and an increase in comedones in the control group [10].

In our study, there was improvement in severity of acne after treatment with antibiotic according to the GEA scale.

A study showed that erythromycin treatment (with zinc acetate) gel showed to be more effective than erythromycin gel (alone) with respect to reducing the number of acne lesions and severity of acne. Number of lesions and severity of acne were significantly reduced at the end of 3rd week in both groups [17]. This showed efficacy of antibiotic in AV treatment.

Topical antibiotics are thought to accumulate in the follicle and may work through both anti-inflammatory and antibacterial effects. Due to increasing antibiotic resistance, monotherapy with topical antibiotics in the management of acne is not recommended. The main topical antibiotics are clindamycin and erythromycin [18].

Ross JI, et al. showed that the widespread use of topical erythromycin and clindamycin to treat acne has resulted in dissemination of cross-resistant strains of propionibacteria [19]. As bacterial antibiotic resistance continues to emerge as a serious global threat, it is crucial that all clinicians re-examine their use of antibiotics. The idea of “no more antibiotics for acne” should at least provoke thoughtful self-appraisal of current prescribing habits for many others [20].

Another study included 96 patients with mild to moderate AV who were treated with 2% alcoholic solution of
azithromycin, erythromycin and clindamycin respectively twice daily for 16 weeks. They reported that there was a statistically significant decrease in inflammatory lesions of acne and comedones with erythromycin treatment [21].

In the current study, our results showed that on laser side, 2 patient showed no improvement and 28 patients showed improvement in the form of: Fair improvement in 4 patients, moderate improvement in 2 patient, marked improvement in 2 patient and excellent improvement in 30 patients. On antibiotic side, 6 patients showed no improvement and 34 patients showed improvement in the form of: Fair improvement in 6 patients, marked improvement in 6 patients, and excellent improvement in 22 patients.

Moreover, the efficacy was investigated by using five antimicrobial regimens for mild to moderate facial acne and whether propionibacterium antibiotic resistance affects treatment response, 649 community participants were allocated one of five antibacterial regimens. The results revealed that 66% of patients expressed moderate or greater improvement at 18 weeks of treatment with topical erythromycin and BPO in a combined formulation [22].

A point of interest, some patients experienced improvement in skin texture and facial tightening with laser sessions. On laser side, patients were more satisfied than antibiotic side. Laser treatment has important advantage of low cost, no side effects, no daily twice application of creams and great efficacy with less relapse. This made our patients more satisfied with laser treatment than with topical antibiotic that caused irritation to some of them and bad compliance of others.

As regard side effects, the current study showed that on laser side, 12 patients showed no side effects and 28 patients experienced side effects in the form of erythema, pigmentation, and relapse. On antibiotic side, 6 patients showed no side effects, and 34 patients experienced side effects in the form of erythema, pigmentation, and relapse.

In a certain study, six patients discontinued their treatment because of undesirable results and experience of deterioration and discomfort, though none of the patients showed any harmful direct side effects from filtered light phototherapy such as burns, pigmented macules, keratosis etc. One patient dropped out after two sessions and the other three dropped out after four to five sessions because of unsatisfactory results as claimed by the patients themselves. Meanwhile, 2 patients refused from continuing the trial, as they did not like to use erythromycin due to undesirable smell and stinging sensation [23]. Side effects though minor includes erythema, peeling, itching, dryness, and burning [24].

Our study showed that laser treatment reduces relapse more than topical antibiotic.

Demina OM and Kartelishev AV, conducted their study to investigate the pathogenic importance of comorbidity for acne recurrence and chronicity as well as to study effectiveness of LLLT. The patients were followed up for 1 year. The results showed a significant reduction in acne score at LLLT treated patients with mild to no recurrence [25].

Our results are compatible with a study that conducted a case control analysis to determine predictors of acne relapse (as defined by receiving an anti-acne medication). A second case–control analysis was performed to determine predictors of receiving a second isotretinoin treatment. The index date of cases was the calendar date of dispensing an anti-acne medication (isotretinoin or systemic antibiotics for 30 days including topical erythromycin, systemic erythromycin). Recurrence rate ratios were estimated using conditional logistic regression. The results showed that being male less than 16 years of age, receiving antibiotics showed greater relapse rate compared to those who received isotretinoin cumulative doses greater than 2450 mg and an isotretinoin treatment longer than 121 days [26].

Previous studies reported that LLLT can modulate acute inflammation and TNFα levels. LLLT appears to be critical for reducing TNFα release [27]. Also, it has the ability to reduce oxidative stress generated by reactive oxygen species [28].

Finally, treatment of inflammatory AV by laser showed great improvement in associated comedonal lesions. With laser treatment, some patients showed better skin texture and tightening of facial skin. Patients were more satisfied with laser treatment as it is safe, effective, cheap with relatively no side effects. Furthermore, laser reduces relapse greatly which is a great drawback of acne.

Treatment of inflammatory AV by laser and topical antibiotic was effective. Laser side showed more improvement than antibiotic side. There was improvement in papulopustular, nodulocystic and associated comedonal lesions. With laser treatment, some patients showed better skin texture and tightening of facial skin. Patients were more satisfied with laser treatment as it is safe, easy applicable and cheap with relatively no side effects, no daily twice application of creams and great efficacy. Laser treatment reduces relapse more than topical antibiotic.

References


Acquired Perforating Dermatosis: Clinical and Histopathological Analysis of 95 Patients From One Center

Yusuf Can Edek¹, Yağmur Aypek¹, Betül Öğüt², Özlem Erdem², Esra Adişen¹

¹ Department of Dermatology, Gazi University Faculty of Medicine, Ankara, Turkey
² Department of Pathology, Gazi University Faculty of Medicine, Ankara, Turkey

Key words: Acquired perforating dermatosis, reactive perforating collagenosis, elastosis perforans serpiginosa, perforating folliculitis, Kyrle disease

Citation: Edek YC, Aypek Y, Öğüt B, Erdem O, Adişen E. Acquired Perforating Dermatosis: Clinical and Histopathological Analysis of 95 Patients From One Center. Dermatol Pract Concept. 2024;14(2):e2024100. DOI: https://doi.org/10.5826/dpc.1402a100

Accepted: December 7, 2023; Published: April 2024

Copyright: ©2024 Edek et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Yusuf Can Edek MD, Department of Dermatology, Gazi University Faculty of Medicine, Emniyet Neighborhood, Mevlana Boulevard, No:29, 06560, Yenimahalle/Ankara. Telephone Number: +903122026129 / +905062818274
E-mail: yusuf-can-35@hotmail.com

ABSTRACT

Introduction: Acquired perforating dermatosis (APD) is a disease group characterized by transepidermal elimination of dermal connective tissue materials such as collagen, elastic fibers, and keratin through the epidermis and observed with pruritic skin lesions.

Objectives: In this study, we aim to clarify the clinical, histopathological, and dermoscopic characteristics of APD, identify the associated systemic disease, and figure out treatment options.

Methods: This study was designed as a single-center retrospective, observational, cross-sectional study. We evaluated all accessible APD cases between January 2004 and June 2022 in a tertiary care hospital.

Results: A total of 95 patients with confirmed APD were included in the study. Sixty percent of the patients were women and 40% were men. The median age at diagnosis was 63.1 years (35-85 years). The most common site of lesions was the lower extremities which were detected in 86.31% of the patients. The concomitant systemic disease was identified in 84.21% of the patients. The most common systemic disease was type 2 diabetes mellitus (65.26%). Antihistamines and topical corticosteroids were the most commonly prescribed treatment agents.

Conclusions: Transepidermal elimination of dermal connective tissue components is a feature of APD and the disease usually presents with pruritic papules and nodules with central keratotic crust or plug. The diagnosis of APD requires a clinical examination and histological investigation. APD is usually accompanied by systemic comorbidities. There are several topical and systemic medications available for APD, however, sometimes the therapy might be challenging.
Introduction

Acquired perforating dermatosis (APD) is a disease group characterized by transepidermal elimination of dermal connective tissue materials such as collagen, elastic fibers, and keratin through the epidermis and observed with pruritic skin lesions. The disease can be divided into 4 different groups: reactive perforating collagenosis (RPC), elastosis perforans serpiginosa (EPS), perforating folliculitis (PF), and Kyrle disease (KD).

The type of dermal connective tissue material is important for classifying diseases. RPC is characterized by the transepidermal elimination of collagen fibers, EPS with elastic fibers, and KD with abnormal keratin. The characteristic lesions of the disease are pruritic umbilicated papules and nodules with a central keratotic crust or plug which often appear on the extensor surfaces of the extremities. Numerous pathways have been identified for APD, but the pathogenesis of transepidermal elimination is still unclear. APD is usually accompanied by systemic diseases like diabetes mellitus, and chronic kidney disease [1-3].

Objectives

In this study, 95 patients with APD who had been diagnosed through clinical and histological investigation were examined. With this investigation, we aim to clarify the clinical, histopathological, and dermoscopic characteristics of APD, identify the associated systemic disease, and figure out treatment options.

Methods

This study was designed as a single-center retrospective, observational, cross-sectional study. We evaluated all accessible APD cases between January 2004 and June 2022 at Gazi University Faculty of Medicine, Department of Dermatology, Ankara, Turkey. The inclusion criteria were being compatible with the APD in the histopathological analysis and clinical examination.

The Gazi University Faculty of Medicine Local Ethical Committee approved the study. The Helsinki Declaration and Guidelines for Good Clinical Practice were used to perform the study, which was done by its most recent revisions. Patients fully informed consent was obtained.

Medical records of patients were retrospectively reviewed and demographic characteristics (gender, age at diagnosis, disease duration), clinical characteristics (disease subtype, distribution of skin lesions, characteristics of lesions, symptoms of patients, Koebner phenomenon, triggering factor of the disease, associated systemic comorbidities, distribution of associated systemic comorbidities by years), histopathological characteristics (analysis of the biopsy specimen, the type of disease, pre-diagnosis of the biopsy specimen), dermoscopic characteristics, and treatment characteristics (topical treatments, phototherapy, systemic treatments) of patients was obtained from dermatopathology records and our hospital database.

Patients were divided into three groups according to treatment response, good response (complete remission of skin lesions and clinical symptoms); partial response (partial disappearance of skin lesions and clinical symptoms); and no response.

Statistical Analysis

IBM SPSS Statistics Version 24.0 was used to perform the statistical analysis (Statistical Package for Social Sciences, SPSS Inc.). Descriptive statistics were used to examine demographic data and disease features. Continuous variables were shown as mean standard deviation (SD), and categorical variables were shown as frequency counts and percentages.

Results

Demographic and Clinical Characteristics

A total of 95 patients with confirmed APD were included in the study. Sixty percent (N = 57) of the patients were women and 40% (N = 38) were men. The median age at diagnosis was 63.1 years (35 - 85 years). The median duration of the disease was 21 months (ranging from 9 days to 30 years). The most common APD type was RPC, 83.15% (N = 79) of the patients, followed by 11.57% (N = 11) with EPS, 3.15% (N = 3) with KD, 2.10% (N = 2) with PF. The most common site of lesions was the lower extremities and was detected in 86.31% (N = 82) of the patients, trunk lesions in 78.94% (N = 75), upper extremities lesions in 68.42% (N = 65), head lesions in 3.15% (N = 3) of the patients. Multiple site involvement was present in 80% (N = 76) of the patients. Hyperkeratotic papules (48.42%, N = 46) and excoriated papules (36.84%, N = 35) were the frequently seen lesions; plaques and nodules were also observed (Figure 1). All patients had symptoms of pruritus, and 6.31% (N = 6) of the patients additionally suffered from pain. Koebner phenomenon was present in 25.26% (N = 24) of the patients.

Investigations for triggering factors revealed scabies history in 7 patients (7.36%), medicines in 5 (5.26%), SARS-CoV-2 vaccines in 2 (2.10%), pregnancy, and SARS-CoV-2 infection in 1 (1.05%) patient for each.
Concomitant Systemic Diseases

The concomitant systemic disease was identified in 84.21% (N = 80) of the patients. The patients associated systemic disorders are listed in Tables 1 and 2. The most common systemic disease was type 2 diabetes mellitus (65.26%, N = 62). 50% (N = 31) of patients with diabetes had been taking insulin, and 38.70% (N = 24) of patients had diabetes-related complications.

Hypertension was the second most common comorbidity and was found in 56.84% (N = 54) of the patients, 45.26% (N = 39) had a cardiovascular disease history, 23.15% (N = 22) of patients had at least one concurrent hepato-biliary disease, 17.89% (N = 17) of the patients had chronic kidney disease, 64.70% (N = 11) received renal replacement therapy (hemodialysis), none of the patients had renal transplantation, 16.84% (N = 16) of the patients had one or more malignancy history, and 25% (N = 4) of these malignancy patients were under active chemotherapy.

The other coexisting diseases included hypothyroidism (7.36%, N = 7), rheumatoid arthritis (3.15%, N = 3), familial Mediterranean fever (2.10%, N = 2), ankylosing spondylitis (1.05%, N = 1), dermatomyositis (1.05%, N = 1), and Gaucher disease (1.05%, N = 1).

Also, we analyzed the distribution of associated systemic comorbidities by years (Figure 2).

Table 1. Associated systemic diseases of patients

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>% (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>65.26% (62)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.84% (54)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>45.26% (39)</td>
</tr>
<tr>
<td>Hepato-biliary disease</td>
<td></td>
</tr>
<tr>
<td>- Hepatitis B infection history</td>
<td>23.15% (22)</td>
</tr>
<tr>
<td>- Cholelithiasis</td>
<td>13.68% (13)</td>
</tr>
<tr>
<td>- Hepatosteatosis</td>
<td>6.31% (6)</td>
</tr>
<tr>
<td>- Cirrhosis</td>
<td>3.65% (3)</td>
</tr>
<tr>
<td>- Hepatitis C infection history</td>
<td>3.65% (3)</td>
</tr>
<tr>
<td>- Wilson disease</td>
<td>1.05% (1)</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td></td>
</tr>
<tr>
<td>- Asthma</td>
<td>18.94% (18)</td>
</tr>
<tr>
<td>- COLD</td>
<td>9.47% (9)</td>
</tr>
<tr>
<td>- Interstitial lung disease</td>
<td>6.31% (6)</td>
</tr>
<tr>
<td>- Chronic kidney disease</td>
<td>3.15% (3)</td>
</tr>
<tr>
<td>Malignancy history</td>
<td>16.84% (16)</td>
</tr>
<tr>
<td>- Colorectal cancer</td>
<td>5.26% (5)</td>
</tr>
<tr>
<td>- Hematological malignancy</td>
<td>4.21% (4)</td>
</tr>
<tr>
<td>- Hepatocellular cancer</td>
<td>3.15% (3)</td>
</tr>
<tr>
<td>- Bladder cancer</td>
<td>1.05% (1)</td>
</tr>
<tr>
<td>- Cutaneous malignancy</td>
<td>1.05% (1)</td>
</tr>
<tr>
<td>- Breast cancer</td>
<td>1.05% (1)</td>
</tr>
<tr>
<td>- Prostate cancer</td>
<td>1.05% (1)</td>
</tr>
<tr>
<td>- Schwannoma</td>
<td>1.05% (1)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7.36%, (7)</td>
</tr>
<tr>
<td>Rheumatological disease</td>
<td>7.36%, (7)</td>
</tr>
</tbody>
</table>
Table 2. Comparison of concomitant systemic diseases of RPC, EPS, KD, and PF

<table>
<thead>
<tr>
<th>Disease (N)</th>
<th>RPC (79 - 83.15%)</th>
<th>EPS (11 – 11.57%)</th>
<th>KD (3 – 3.15%)</th>
<th>PF (2 – 2.10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus (62)</td>
<td>52 (83.87%)</td>
<td>6 (9.67%)</td>
<td>3 (4.83%)</td>
<td>1 (1.61%)</td>
</tr>
<tr>
<td>Hypertension (54)</td>
<td>46 (85.18%)</td>
<td>5 (9.25%)</td>
<td>2 (3.70%)</td>
<td>1 (1.85%)</td>
</tr>
<tr>
<td>Cardiac Disease (39)</td>
<td>31 (79.48%)</td>
<td>4 (10.25%)</td>
<td>3 (7.69%)</td>
<td>1 (2.56%)</td>
</tr>
<tr>
<td>Hepato-Biliary Disease (22)</td>
<td>15 (68.18%)</td>
<td>5 (22.72%)</td>
<td>1 (4.54%)</td>
<td>1 (4.54%)</td>
</tr>
<tr>
<td>Pulmonary Disease (18)</td>
<td>13 (72.22%)</td>
<td>4 (22.22%)</td>
<td>1 (5.55%)</td>
<td>-</td>
</tr>
<tr>
<td>Chronic Kidney Disease (17)</td>
<td>14 (82.35%)</td>
<td>-</td>
<td>2 (11.76%)</td>
<td>1 (5.88%)</td>
</tr>
<tr>
<td>Malignancy (16)</td>
<td>11 (68.75%)</td>
<td>3 (18.75%)</td>
<td>2 (12.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypothyroidism (7)</td>
<td>5 (71.42%)</td>
<td>2 (28.57%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

EPS = elastosis perforans serpiginosa; KD Kyrle disease; PF = perforating folliculitis; RPC = reactive perforating collagogenosis.

Figure 2. Distribution of associated systemic comorbidities by years.

Histopathological Characteristics

All patients (100%, N 95) had histopathological findings compatible with diagnosis of APD. In the histopathological analysis, basophilic debris was observed in all of the biopsy specimens. 78.94% of the biopsy specimens transdermal collagen fiber elimination, 11.57% of the biopsy specimens transepidermal elastic fiber elimination, and 3.15% of the biopsy specimens transdermal both collagen and elastic fiber elimination was detected (Figure 3).

After evaluating the pre-diagnosis of the biopsy specimens, in 69.74% (N = 66) of the biopsy specimens, where APD was suspected, other common pre-diagnosis was dermatitis herpetiformis (25.26%, n = 24), scabies (18.94%, N = 18), bullous pemphigoid pre-bullous stage (17.89%, N = 17), pityriasis lichenoides et varioliformis acuta (PLEVA) (16.84%, N = 16), neurotic excoriation (14.73%, N = 14) and prurigo nodularis (13.68%, N = 13).

Dermoscopic Characteristics

Dermoscopic analysis of 41 lesions from 18 patients was obtained (Table 3). Central keratotic plug was the common finding (100%), also white irregular halo (60.97%), peripheral erythematous zone (60.97%), thin scale ring surrounding the lesion (51.21%), and altered hair shaft (41.46%) were among the commonly seen characteristic. Dotted-linear (26.82%), hairpin (26.82%), and glomerular (4.87%) vessels were detected in the dermoscopic analysis of APD lesions (Figure 4).
Figure 3. (A-C) A case with elastic and collagen fiber alteration from the epidermis. (A) Epidermal ulceration and basophilic inflammatory debris are observed (H&E stain). (B) Collagen fiber penetration into the epidermis was observed as red (arrow) and elastic fiber penetration was observed as black fiber (arrowhead) with Elastic Von Gieson (EVG) staining. (C) With Masson trichrome stain, green-colored (arrow) collagen fiber alteration was observed from the epidermis to the dermis perpendicularly. (D-F) In a case with only collagen fiber alteration from the epidermis (D). Ulceration and basophilic debris were observed (H&E stain). (E) Fibers altered from the epidermis in EVG stain are red (arrows), f. Green is traced in Masson trichrome stain (arrows). (G) In a case with only elastic fiber altered from the epidermis. (H) Epidermal hyperplasia (H&E stain). Fibers altered from the epidermis in the EVG stain were observed in black, perpendicular to the dermis (arrows).

Table 3. Dermoscopic analysis of acquired perforating dermatosis patients in our study

<table>
<thead>
<tr>
<th>Dermoscopic Feature</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central keratotic plug</td>
<td>41</td>
<td>100%</td>
</tr>
<tr>
<td>White halo surrounding the lesion</td>
<td>25</td>
<td>60.97%</td>
</tr>
<tr>
<td>Peripheral erythematous zone</td>
<td>25</td>
<td>60.97%</td>
</tr>
<tr>
<td>Thin scale ring surrounding the lesion</td>
<td>21</td>
<td>51.21%</td>
</tr>
<tr>
<td>Altered hair shaft</td>
<td>17</td>
<td>41.46%</td>
</tr>
<tr>
<td>Dotted and linear vessels distribution radially</td>
<td>11</td>
<td>26.82%</td>
</tr>
<tr>
<td>Peripheral hairpin vessels</td>
<td>11</td>
<td>26.82%</td>
</tr>
<tr>
<td>Peripheral striation</td>
<td>11</td>
<td>26.82%</td>
</tr>
<tr>
<td>Peripheral hyperpigmentation</td>
<td>10</td>
<td>24.39%</td>
</tr>
<tr>
<td>Focal red dots/globules</td>
<td>6</td>
<td>14.63%</td>
</tr>
<tr>
<td>Peripheral glomerular vessels</td>
<td>2</td>
<td>4.87%</td>
</tr>
<tr>
<td>Pigment network-like area</td>
<td>2</td>
<td>4.87%</td>
</tr>
<tr>
<td>Peripheral pigment network</td>
<td>1</td>
<td>2.43%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>2.43%</td>
</tr>
<tr>
<td>Red background</td>
<td>1</td>
<td>2.43%</td>
</tr>
</tbody>
</table>
We also observed cases of EPS (11.57%), KD (3.15%), and PF (2.10%).

Clinical examination plus histopathological analysis are gold-standard methods for the diagnosis of APD [1-3]. Characteristic lesions are umbilicated papules and nodules with central keratotic crust or plug. The most common lesions in our study were excoriated and hyperkeratotic papules, also with plaques and nodules. The lower extremity was the most commonly affected area in our study (86.31%) and it was similar to the literature [4,6,7,9-11]. Koebnerization such as linear localized lesions in the excoriated skin are observed in the APD and were detected in 25.26% of our patients. Other studies have reported different frequencies for the Koebner phenomenon (31% - 56%) [4,6]. Similar to the complaints of our patients, pruritus is the most common reported symptom of APD. However, pain which was experienced by 6.31% of our patients is also a reported symptom.

The pre-diagnosis of biopsy specimens in our study showed that APD was suspected in 68.28% (N = 56) of the patients, and dermatitis herpetiformis, scabies, bullous pemphigoid pre-bullous stage, PLEVA, neurotic excoriation, and prurigo nodularis were among the other common suspected diseases. APD is characterized by hyperkeratosis of stratum corneum, hyperplasia of the epidermis, central basophilic plug, basophilic debris, and transepidermal elimination of connective tissue materials, these features help to

**Treatment and Outcome Characteristics**

Antihistamines and topical corticosteroids were the most commonly prescribed treatment agents (both 83.15%, N = 79) also, topical dapsone 2.10% (N = 2), topical retinoids 2.10% (N = 2), and topical calcineurin inhibitors 1.05% (N = 1) were used for treatment.

Systemic steroid treatment was applied in 31.57% (N = 30) of the patients, systemic retinoids (4.21%, N = 4), omalizumab (2.10%, N = 2), methotrexate (1.05%, N = 1), allopurinol (1.05%, N = 1) were also prescribed to patients. Photodynamic therapy was another treatment option and was used in 24.21% (N = 23) of the patients.

After treatment 35.78% (N = 34) of the patients had a complete response, 50.52% (N = 48) of the patients showed partial response and 10.52% (N = 10) of the patients had no response. Also, 5 patients (6.09%) died during the follow-up due to underlying systemic disease.

**Conclusions**

In this study we describe a case series of APD which involved 95 patients. In our patient cohort, RPC was the most common form of APD and occurred in 83.15% of the patients. We also observed cases of EPS (11.57%), KD (3.15%), and PF (2.10%).

Clinical examination plus histopathological analysis are gold-standard methods for the diagnosis of APD [1-3]. Characteristic lesions are umbilicated papules and nodules with central keratotic crust or plug. The most common lesions in our study were excoriated and hyperkeratotic papules, also with plaques and nodules. The lower extremity was the most commonly affected area in our study (86.31%) and it was similar to the literature [4,6,7,9-11]. Koebnerization such as linear localized lesions in the excoriated skin are observed in the APD and were detected in 25.26% of our patients. Other studies have reported different frequencies for the Koebner phenomenon (31% - 56%) [4,6]. Similar to the complaints of our patients, pruritus is the most common reported symptom of APD. However, pain which was experienced by 6.31% of our patients is also a reported symptom.

The pre-diagnosis of biopsy specimens in our study showed that APD was suspected in 68.28% (N = 56) of the patients, and dermatitis herpetiformis, scabies, bullous pemphigoid pre-bullous stage, PLEVA, neurotic excoriation, and prurigo nodularis were among the other common suspected diseases. APD is characterized by hyperkeratosis of stratum corneum, hyperplasia of the epidermis, central basophilic plug, basophilic debris, and transepidermal elimination of connective tissue materials, these features help to
differentiate it from prurigo nodularis, granuloma annulare, sarcoidosis, and infections [1,2,4].

Recently, Wang et al published a study on dermoscopic analysis of APD lesions in 39 patients and determined central homogeneous structureless area, dotted and linear vessels, and white halo periphery at the lesion among the most common characteristics of APD lesions [12]. In our study central keratotic plug, white halo surrounding the lesion, and peripheral erythematous zone were the most commonly observed dermoscopic features, also dotted, linear, hairpin, and glomerular vessels were detected. Elmas et al evaluated 60 lesions from 7 patients and identified the histopathologic counterpart of the dermoscopic analysis [13]. The central yellow-brown structureless area corresponded to the central keratin crust, peripheral white rim to invaginating epidermal hyperplasia, white structureless area to fibrotic collagen accumulation in the dermis, peripheral dotted vessels to superficial dilated vessels, and brown reticular lines to hyperpigmented basal keratinocytes [13]. Dermoscopy may be an alternative diagnostic tool in APD patients.

The pathogenesis of the disease is still unclear, and several factors have been identified. Vasculopathy, hypoxic conditions, and superficial trauma in genetically susceptible individuals can trigger necrobiosis of collagen fibers in the dermis and result in transepidermal elimination of these fibers, which is the main component of the disease. Additionally, increased toxic metabolites, oxidative stress, and advanced glycation end products may cause collagen cross-linking and abnormal collagen formation. Akoğlu et al investigated receptors of advanced glycation end products in the biopsy materials from APD patients and compared them with the healthy control group, and observed overexpression of receptors in endothelial cells, fibroblasts, and inflammatory cells of the dermis in APD patients [8]. Also, to understand the molecular pathogenesis of the disease, Gambichler et al analyzed lesional and perilesional CD34, matrix metalloproteinase-1 (MMP-1), tissue inhibitor of metalloproteinases-1 (TIMP-1), transforming growth factor-β3 (TGF-β3) levels [14]. Compared to perilesional skin, endothelial cells showed decreased CD34 immunoreactivity that indicates vascularization defect of lesions and also increased TGF-β3, MMP-1, and TIMP-1 activity that can be associated with altered extracellular matrix metabolism has been detected in the lesional skin [14]. TGF-β overexpression also has roles in fibrosis, case reports of concomitant APD and diseases characterized by fibrosis have been published. TGF-β may be effective both on tissue fibrosis and tissue remodeling on APD [17]. In this study, we detected one APD patient with pulmonary fibrosis.

Because APD is frequently associated with systemic comorbidities such as diabetes mellitus, chronic kidney diseases, malignancies, and endocrinological diseases, it is important to consider and question patients in terms of concomitant systemic diseases (Table 4) [15,16,33-35]. In our study, 84.21% of the patients had at least one concurrent systemic disease; the most common diseases include diabetes mellitus, hypertension, and cardiovascular diseases.

Kawakami et al reported that diabetic microangiopathy may be a triggering factor for APD and theorized that a combination of trauma and dermal necrosis due to decreased blood flow secondary to diabetic microangiopathy may be an important factor in the pathogenesis of APD [15]. Diabetic complications such as neuropathy, nephropathy, and retinopathy are suggestive of diabetic microangiopathy [15]. All these point to the need to evaluate diabetic patients with APD in terms of diabetic complications. In this study, we observed 62 patients with type 2 diabetes mellitus, 38.70% of whom had diabetes-related complications. The mean HbA1c level was 7.70% (4.4% - 16.4%). Our findings also support the diabetic microangiopathy theory.

Morton et al observed APD patients with chronic kidney disease and theoretically explained skin changes secondary to renal failure, such as calcium microdeposition in the dermis, may lead to inflammatory response and connective tissue degradation, which can be observed in the APD pathogenesis [16]. In our study 17.89% of the patients had chronic kidney disease, and 64.70% of these patients were on hemodialysis.

Malignancies are one of the commonly detected comorbidities in APD patients [32,33]. In our study, 16.84% of the patients had a history of malignancy; colorectal cancer (31.25%), hematologic malignancies (25%), and hepatocellular cancer (18.75%) were the most common accompanying malignancies. Singh et al published a patient with APD associated with mediastinal synovial sarcoma [32]. Increased TGF-β3 has been shown in APD skin specimens, and mesenchymal stem cells secrete growth factors such as TGF-β3. It is theorized that cytokines such as TGF-β3 may be a connection between APD and mesenchymal tumors [32].

Similar to our observation in our patient cohort, patients with APD may also have concurrent conditions such as hypothyroidism, infections, and pulmonary, hepatobiliary, and rheumatological diseases, all of which are thought to have a role in the pathogenesis of the disease [33,35].

Various factors are believed to trigger APD, including medicines, pregnancy, trauma, and scabies [18,26]. APD cases secondary to the use of tyrosine kinase inhibitors, tumor necrosis factor-α (TNF-α) inhibitors, VEGF inhibitors, and epidermal growth factor receptor (EGFR) inhibitors have been published [18,24-26]. Gilaberte et al reported a PF after TNF-α inhibitors (infliximab) treatment in a patient with rheumatoid arthritis [25]. There are several theories about how TNF-α inhibitors contribute to the pathophysiology of APD, including the idea of blocking TNF-α may
<table>
<thead>
<tr>
<th>Study</th>
<th>Country – Year</th>
<th>Patient Number (Female/Male)</th>
<th>Mean Age at Onset (years)</th>
<th>Mean Duration of Disease (month)</th>
<th>Most Common Localisation</th>
<th>Positive Koebner Phenomenon (N-%)</th>
<th>Concurrent Systemic Disease (N-%)</th>
<th>Comorbidities (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saray et al [4]</td>
<td>Turkey – 2006</td>
<td>22 (6/16)</td>
<td>49</td>
<td>6.2</td>
<td>Lower Extremity</td>
<td>7 – 31.8%</td>
<td>CKD (16), DM (11), Hepatitis (6), Hypothyroidism (2), Renal Transplant Recipients (2), Tuberculosis (1), Graft-versus-host Disease (1), Cardiovascular Disease (1), Rheumatoid arthritis (1)</td>
<td></td>
</tr>
<tr>
<td>Satti et al [5]</td>
<td>Saudi Arabia – 2010</td>
<td>15 (12/3)</td>
<td>50</td>
<td>6</td>
<td>Lower Extremity</td>
<td>-</td>
<td>CKD (9), DM (9), Hypertension (9), Hepatitis (3), Pulmonary Disease (3), Rheumatoid Arthritis (3), Thyroid Disease (3), Malignancy (2), Infection (2)</td>
<td></td>
</tr>
<tr>
<td>Akoglu et al [6]</td>
<td>Turkey – 2013</td>
<td>25 (11/14)</td>
<td>51.8</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
<tr>
<td>Kim et al [7]</td>
<td>Korea - 2014</td>
<td>30 (18/12)</td>
<td>55.5</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
<tr>
<td>Akoglu et al [8]</td>
<td>Turkey – 2016</td>
<td>41 (25/16)</td>
<td>51</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
<tr>
<td>García-Malinis et al [9]</td>
<td>Spain – 2017</td>
<td>31 (19/12)</td>
<td>54</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
<tr>
<td>Garrido et al [10]</td>
<td>Portugal – 2019</td>
<td>57 (28/29)</td>
<td>63.1</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
<tr>
<td>Gore Karaci et al [11]</td>
<td>Turkey – 2020</td>
<td>80 (49/31)</td>
<td>58.4</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
<tr>
<td>Eckel et al (this study)</td>
<td>Turkey – 2022</td>
<td>95 (57/38)</td>
<td>63.1</td>
<td>3</td>
<td>Lower Extremity</td>
<td>11 – 36.6%</td>
<td>CKD (12), DM (12), Cardiovascular Disease (9), Pulmonary Disease (6), Psoriasis (1), Vitiligo (1)</td>
<td></td>
</tr>
</tbody>
</table>
cause fibronectin accumulation, which may contribute by stimulating epithelial migration and proliferation [25]. In our study, we observed one patient under etanercept treatment for ankylosing spondylitis presenting with generalized pruritic lesions and diagnosed with APD after histopathologic analysis.

Healy et al. and Eriyagama et al. reported pregnant patients with pruritic skin lesions with APD diagnoses [19,20]. We observed a patient who developed APD after pregnancy. APD should be considered among the pruritic pregnancy dermatosis.

Various APS case reports following scabies have been published. Intense scratching during scabies infection can cause superficial skin microtrauma and transepidermal elimination of dermal materials [22,23]. In addition to case reports of APD occurring following scabies, 7.36% of the patients in our study had scabies history of previous scabies infection.

One of our patients with hypothyroidism and coronary artery disease developed RPC one month after the second dose of CoronaVac (Sinovac) vaccine. Another patient with known coronary artery disease, hypertension, and diabetes mellitus had RPC two months after the second dose of CoronaVac (Sinovac) vaccine. SARS-CoV-2 vaccines have been linked to various cutaneous manifestations such as lichen planus, bullous pemphigoid, psoriasis, and cutaneous vasculitis [27-30]. So far, no cases of APD have been reported after SARS-CoV-2 vaccines. Considering the comorbidities of these patients it is difficult to build such a relationship between APD and SARS-CoV-2 vaccines. Immune dysregulation and increased cytokine levels triggered by viral components and adjuvants of SARS-CoV-2 vaccines may take part in the pathogenesis of APD.

Treatment of APD may be challenging, sometimes it may require a combination of therapies. Treatment modalities include topical-intralesional-systemic steroids, antihistamines, topical-oral retinoids, and phototherapy [36]. While choosing treatment the accompanying systemic diseases should be considered. Additionally, new medicines such as allopurinol, and dupilumab should be considered for the treatment of resistant patients. As in other reports in the literature, topical steroid and antihistamine combination was the most common treatment in our study (Table 5) [10].

In the literature and treatment guidelines, phototherapy has been recognized as one of the effective treatment options for APD [37,38]. Mechanisms of antipruritic effects of phototherapy include mast cell suppression, and reduced epidermal nerves decreasing TGF-β expression, which is important in APD pathogenesis. UV light may exert its effects by inhibiting neutrophil infiltration, which is characteristic in the early stage of APD, or neutrophils secretion of MMP that is involved in APD by digesting the extracellular matrix and destroying the basement membrane [37].

Systemic retinoids are one of the options in APD treatment, in our study acitretin was used in four patients, one of them (25%) had a complete response, however, three patients had a partial response.

Allopurinol recently has shown success in APD treatment in the case reports. Allopurinol may be effective in APD treatment via decreasing oxygen-free radicals, crosslinking of collagen fibers secondary to advanced glycation, and skin necrosis by inhibition of the xanthine-oxidase enzyme [39-43]. In our study, allopurinol was used in one patient with chronic kidney disease, congestive heart failure, hyperuricemia, and diabetes mellitus after treatment complete regression of APD lesions was observed.

The limitation of this study is its retrospective design. To the best of our knowledge, this study is the longest-term and largest case series in the literature.

Transepidermal elimination of dermal connective tissue components is a feature of APD and the disease usually presents with pruritic papules and nodules with central keratotic crust or plug. Various factors like medicines, trauma, pregnancy, and scabies can be the etiological agent of the disease.

### Table 5. Treatments and outcomes of the patients

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Corticosteroids and Antihistamines (79)</td>
<td>25.31%</td>
<td>43.03%</td>
<td>31.64%</td>
</tr>
<tr>
<td>Systemic Steroids (30)</td>
<td>23.33%</td>
<td>36.66%</td>
<td>30%</td>
</tr>
<tr>
<td>Phototherapy (23)</td>
<td>26.08%</td>
<td>56.52%</td>
<td>17.39%</td>
</tr>
<tr>
<td>Systemic Retinoids (4)</td>
<td>25%</td>
<td>75%</td>
<td>-</td>
</tr>
<tr>
<td>Omalizumab (2)</td>
<td>-</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Topical Dapsone (2)</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Topical Retinoids (2)</td>
<td>-</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Topical Calcineurin Inhibitors (2)</td>
<td>-</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Methotrexate (1)</td>
<td>-</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Allopurinol (1)</td>
<td>100%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Although the etiology of the disease is still unclear, several theories such as vasculopathy, hypoxia, superficial trauma, and oxidative stress have been put out to explain it. The diagnosis of APD requires a clinical examination, histological investigation, and dermoscopic analysis, which may also be useful. APD is usually accompanied by systemic comorbidities. There are several topical and systemic medications available for APD, however, sometimes the therapy might be challenging. The clinical, histopathological, dermoscopic, and therapeutic features of 95 patients were examined in this study. Future case reports and studies can help us in identifying the characteristics of APD.

References


Combining Reflectance Confocal Microscopy, Optical Coherence Tomography and Ex-Vivo Fluorescence Confocal Microscopy for Margin Assessment in Basal Cell Carcinoma Excision

Simone Michelini¹, Victor Desmond Mandel², Marco Ardigò³, Silvana Ciardo³, Carlo Cota², Anna Maria Cesinaro⁴, Elena Rossi³, Barbara Ferrari¹, Shaniko Kaleci³, Marco Di Fraia¹, Camilla Chello¹, Carmen Cantisani¹, Federica Trovato¹, Caterina Longo³⁵, Giovanni Pellacani¹

1 Dermatologic Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, La Sapienza University of Rome, Rome, Italy
2 Porphyria and Rare Diseases Unit, San Gallicano Dermatological Institute - IRCCS, Rome, Italy
3 Dermatology Unit, Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
4 Department of Anatomic Pathology, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy
5 Centro Oncologico ad Alta Tecnologia Diagnostica, Azienda Unità Sanitaria Locale - IRCCS, Reggio Emilia, Italy

Key words: BCC, margin assessment, RCM, OCT, FCM ex-vivo


Accepted: October 22, 2023; Published: April 2024

Copyright: ©2024 Michelini et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. Simone Michelini and Victor Desmond Mandel equally contributed to this manuscript and should be considered co-first authors.

Corresponding Author: Dr. Simone Michelini, Dermatologic Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, La Sapienza University of Rome, Viale del Policlinico n° 155, zip code 00161, Rome, Italy. e-mail: simone.michelini@uniroma1.it

ABSTRACT

Introduction: Recent developments of noninvasive, high-resolution imaging techniques, such as reflectance confocal microscopy (RCM) and optical coherence tomography (OCT), have enhanced skin cancer detection and precise tumor excision particularly in highly aggressive and poorly defined basal cell carcinomas (BCCs).

Objectives: The aim of this pilot study is to assess the feasibility and reproducibility of a systematic clinical workflow combining noninvasive (RCM-OCT) and invasive fluorescence confocal microscopy (FCM) imaging modalities in pre- and intra-surgical evaluations of the lateral and deep margins of
**Methods:** Superficial incisions were made 2 mm beyond the clinical-dermoscopic BCC margins. Lateral margins were then explored with OCT and RCM. In positive margins, a further cut was made 2 mm distal from the previous. A final RCM/OCT-based double-negative margin was drawn around the entire perimeter of the lesion before referring to surgery. The freshly excised specimen was then examined with FCM (ex-vivo) for the evaluation of the deep margin. Histopathologic examination eventually confirmed margin involvement.

**Results:** The study included 22 lesions from 13 patients. At the end of the study, 146 margins—106 negative (73%) and 40 positive (27%) at RCM/OCT—were collected. The RCM/OCT margin evaluation showed an overall sensitivity of 100% and a specificity of 96.3%. The overall positive margins diagnostic accuracy was 98.2%. Reproducibility was evaluated on recorded images and the raters showed a substantial inter-observer agreement on both RCM (κ = 0.752) and OCT images (κ = 0.724).

**Conclusions:** The combined RCM/OCT/FCM ex-vivo approach noninvasively facilitates the presurgical and intrasurgical lateral and deep margin assessment of poorly defined BCCs.

**Introduction**

Basal cell carcinoma (BCC) is a widely diffused neoplasm in western countries with an increasing incidence as a consequence of inappropriate sun exposure and increased longevity of the population. Although many different minimal to noninvasive procedures have been proposed and applied in selected cases [1], surgical excision remains the recommended treatment option achieving average 5-year disease-free rates of over 98% for BCCs [2].

According to the National Comprehensive Cancer Network (NCCN), the recommended lateral margin for BCCs is 4 mm which should be extended in case of high-risk BCCs, such as sclerosing, infiltrative or micronodular BCCs, because of the higher rate of recurrence. Mohs micrographic surgery (MMS) in its original form or in its variants (i.e. spaghetti technique, Tubingen torte, slow-Mohs) represents the best treatment option in terms of margin clearance and recurrence rate in these clinical situations [3]. However, due to MMS highly specialized and expensive requirements, this procedure is not available everywhere.

In the last decades, the development of non-invasive, high resolution imaging techniques, such as reflectance confocal microscopy (RCM) and optical coherence tomography (OCT), allowed the possibility to explore the tissue in vivo at nearly histologic resolution, significantly improving skin cancer diagnostic accuracy. As a consequence, due to shallow imaging penetration, the use of these techniques has also been proposed for lateral margin assessment in lentigo maligna and BCC [4,5-10]. Additionally, ex-vivo fluorescence confocal microscopy (FCM) is an emerging imaging technique that allows real-time microscopic examination of freshly excised cutaneous tissue. Thanks to its procedural simplicity and digital histopathologic acquisition rapidity, this tool is mainly applied to intra-operative analysis of the surgical margins of BCC in a MMS-like setting, as it is able to observe the entire skin specimen and both superficial and deeper margins with a very high accuracy [11].

The combined use of highly performing invasive and non-invasive imaging methods may enhance the capabilities for skin cancer detection and precise tumor excision particularly useful in highly aggressive and poorly defined BCCs in order to guarantee radical treatment whilst saving procedural time and costs.

**Objectives**

The aim of this pilot study is to assess the feasibility and reproducibility of an organized and systematic clinical workflow combining non-invasive (RCM-OCT) and invasive (FCM) imaging modalities in the pre- and intra-surgical evaluation of lateral and deep margins.

**Methods**

Patients presenting lesions with a confirmed clinical, dermoscopic and RCM diagnosis of BCC were recruited from the outpatient dermatology clinics of San Gallicano Dermatological Institute of Rome and University of Modena and Reggio Emilia.

Inclusion criteria were to present (i) at least one lesion with clinical, dermoscopic or RCM diagnosis of primary BCC; (ii) poorly defined lateral borders and/or clinical features suggesting sclerosing or infiltrating forms; (iii) lesion fully accessible for examination with RCM and OCT; (iv) patients >18 years old (v) patient willingness to participate. Exclusion criteria were: (i) crusted or ulcerated lesions, (ii) local relapses or previously treated lesions; (iii) lesions located on anatomical sites not allowing a proper evaluation
with RCM/OCT (eg nose wings, eyelid margins, auricles etc.); (iv) incapability to understand and sign the informed consent. Written informed consent was collected from all the participants.

**Imaging Procedure**

Prior to mapping procedure, all patients underwent a clinical, dermoscopic (Dermlite HR, DL4W magnification 10x) and hand-held RCM (Vivascope 3000® Vivascope GmbH) evaluation to confirm BCC diagnosis. The lesion mapping procedure consisted of 4 steps, adapted on the “SMART” approach previously proposed for skin tumor mapping, as follows [12,13]:

**Step 1.** Clinical dermoscopic margin marking. After lesion inspection, visible BCC margins were delimited in hexagonal or rhomboidal shaped margins around the tumor (depending on the size and shape) to facilitate the subsequent surgical procedure, and marked with an ink pen 2 mm beyond the clinically and dermoscopically determined borders.

**Step 2.** Margin superficial cut. After 1 hour of occlusive application of topical anesthetic, (lidocaine 25 mg/g + prilocaine 25 mg/g), a superficial cut was made with a scalpel (blade#15), overlying the dermo-graphic pen ink. In case of bleeding, it was readily arrested with sterile gauze soaked in tranexamic acid.

**Step 3.** Lateral Margin exploration with non-invasive techniques.

Margins were assessed by combining the information from both OCT and RCM. OCT imaging was carried out by Vivosight D-OCT (Michelson Diagnostics) as previously described [14,15]. RCM margins were explored with a hand-held RCM Vivascope 3000 in live mode [12,13]. The imaging procedure started from the center of the lesion outwards in a radial direction up to the visualization of the superficial cut for each margin with both techniques. A margin was considered “positive” if presenting OCT or RCM BCC specific features less than 1mm inward or outward from the cut. OCT BCC positive features corresponded to the “Berlin Score” system [16], and RCM ones corresponded to the features enlisted by Longo et al. (dark silhouettes, bright tumor islands/cords, cleft-like dark spaces, dendritic cells, increased vascularization) [6]. In case of a positive margin, a further cut was made 2 mm distal from the previous or at an estimated 2 mm distance from the outermost visible BCC structure, repeating the procedure in case of...

---

**Figure 1.** The procedure in clinical (A) and dermoscopic (B) detail. With an ink pen, visible BCC margins were defined around the tumor in a hexagonal or rhomboidal form 2 mm beyond the clinically and dermoscopically confirmed limits. A shallow incision was made over the dermographic pen ink. (C) An OCT scan shows basaloid islands (asterisks) extending beyond the first incision (red arrow). The margin has then been advanced by 2 mm (white arrow).
Figure 2. RCM exploration confirmed the presence of basaloid islands (asterisk) near the margin (white arrow).

a further positive margin. A final RCM/OCT-based double negative margin was drawn around the entire perimeter of the lesion before referring to surgery.

All OCT and RCM margin imaging were acquired as a multilayer tiff file and an AVI video file, respectively, for reproducibility study (Figures 1 and 2).

Step 4. Surgical procedure and deep margin check. Patients proceeded to surgery following the RCM/OCT annotated margins. After specimen excision, the freshly excised specimen was prepared for the FCM (ex vivo) imaging procedure for intra-operative margin evaluation:

- FCM of deep margin: FCM imaging was performed with VivaScope 2500 4th Gen® (MA-VIG GmbH) following the previously described procedure. [17] Along the side of the polygonal shaped specimen thin transversal sections were cut from the epidermal surface to the bottom of the excised specimen. The remaining central portion of the specimen and the lateral sections were prepared for FCM imaging. The bottom of the central portion was first imaged for the evaluation of the deep margin. Subsequently, each lateral section was imaged positioning the specimen facing the internal side, on the device glass plate. A board-certified dermatologist (M.A.), experienced in reading FCM imaging, evaluated BCC margin involvement. In case of BCC positive margin, the surgical cut was selectively enlarged in the positive sector.

After negative FCM margin confirmation, surgical breach closure is performed. Histopathologic examination was sent to a board-certified pathologist (C.C., A.M.C.) to confirm the diagnosis and margin involvement (Fig3).

Follow-up study. After 1 year from excision, patients underwent clinical and dermoscopic examination of the scar and its peripheral area in order to identify possible BCC recurrence.

Reproducibility Study

To validate reproducibility of RCM/OCT reading procedure, all the RCM imaging videos and the OCT images from all the margins evaluated were randomized and retrospectively evaluated by two external readers, blinded to any dermoscopic, clinical and histopathologic information.

The external readers were asked to evaluate RCM and OCT margin as positive or negative, separately.

Statistical Analysis

As descriptive statistics, absolute numbers and percentages of true positive, true negative, false positive and false negative margins have been reported along with sensitivity and specificity values. The diagnostic positive margins performance is evaluated on the receiver operating characteristic (ROC) curve and the area under the curve.

The Cohen kappa ($\kappa$) statistic has been used to measure the agreement between the histologic positive margin and the two “in vivo” instruments. Moreover, $\kappa$ was also calculated in the evaluation of the agreement between the final operator positive margins and histological positive margins. We evaluated inter-observer agreement for positive margins in both RCM and OCT evaluations in relation to the golden standard. The interpretation of agreement adopted here is less than chance agreement ($\kappa < 0$), slight agreement ($\kappa = 0.01-0.20$), fair agreement ($\kappa = 0.21-0.40$), moderate agreement ($\kappa = 0.41-0.60$), substantial agreement ($\kappa = 0.61-0.80$), and almost perfect agreement ($\kappa = 0.81-0.99$). The interpretation of reproducibility adopted is marginal ($\kappa = 0.00-0.40$), good ($\kappa = 0.40-0.75$) and excellent ($\kappa >0.75$). For all analyses, a $P < 0.001$ was considered statistically significant. STATA program version 14 (StataCorp) was used to perform statistical analysis.

Results

The study included a total of 146 margins from 22 lesions from 13 patients, 4 females (30.8%) 9 males (69.2%), median age 71.4 years (range: 47-90 years), enrolled between June 2021 and November 2021 at the San Gallicano
Figure 3. (A) Introperative axial FCM image of an excisional biopsy in fluorescence mode. Reflectance mode (B) and combined mode (C) showing multiple basaloid islands of a preauricular BCC. En face view highlighting the superficial cut (white arrows) in Fluorescence mode (D) reflectance mode (E) and combined mode (F). Deep margin showed no BCC feature in FCM. (G) Histology image displaying the margin cut (black arrow) close to the BCC.
The RCM/OCT margin evaluation showed an overall sensitivity of 100% and a specificity of 96.3% and an overall positive margins diagnostic accuracy was 98.2%.

Concerning diagnostic accuracy, the percentages of agreement with histopathology was higher for the first rater, reaching 95.7% accuracy for RCM ($\kappa = 0.89$) and 95.1% for OCT ($\kappa = 0.87$), than the second one, reaching 91.5% and 89.4% ($\kappa = 0.76$ and $\kappa = 0.71$), respectively (Table 1). Reproducibility was evaluated on recorded images, and the raters showed a substantial inter-observer agreement on both RCM ($\kappa = 0.751$) and OCT images ($\kappa = 0.724$) (Table 2).

Ex vivo FCM deep margin check. All deep margins resulted negative in histopathology as well as in ex vivo FCM imaging.

Follow-up study. After one-year follow-up no recurrences have been observed in clinical and dermoscopic evaluation.

**Conclusions**

The aim of our study was the evaluation of the impact of the in vivo tumor lateral margin assessment in a presurgical phase using RCM/OCT method combined and the ex-vivo

---

**Table 1. Lateral Margin Exploration With Non-Invasive Techniques, Correlation With Histopathology and Reproducibility**

<table>
<thead>
<tr>
<th></th>
<th>Histology</th>
<th>% of correct diagnosis</th>
<th>K-value</th>
<th>Level of agreement</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCM</strong></td>
<td>Negative</td>
<td>105</td>
<td>0</td>
<td>97.2</td>
<td>0.924</td>
<td>0.982</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>4</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OCT</strong></td>
<td>Negative</td>
<td>105</td>
<td>0</td>
<td>97.2</td>
<td>0.924</td>
<td>0.982</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>4</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rater 1</strong></td>
<td>RCM</td>
<td>Negative</td>
<td>103</td>
<td>0</td>
<td>95.7</td>
<td>0.888</td>
<td>0.972</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>6</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OCT</strong></td>
<td>Negative</td>
<td>103</td>
<td>1</td>
<td>95.1</td>
<td>0.868</td>
<td>0.957</td>
<td>96.9</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>6</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rater 2</strong></td>
<td>RCM</td>
<td>Negative</td>
<td>104</td>
<td>7</td>
<td>91.5</td>
<td>0.758</td>
<td>0.871</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>5</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OCT</strong></td>
<td>Negative</td>
<td>100</td>
<td>6</td>
<td>89.4</td>
<td>0.713</td>
<td>0.867</td>
<td>81.8</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>9</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^4$ margins histologically result not evaluable.

AUC = area under the curve; OCT = optical coherence tomography; RCM reflectance confocal microscopy.

First and second rater evaluation for RCM and OCT of margins compared to histological diagnoses, the percentage of correct diagnoses, $\kappa$ value, the level of agreement, the sensitivity, the specificity, and ROC area for both raters.
Table 2. Agreement Between Operators

<table>
<thead>
<tr>
<th></th>
<th>RCM rater 1</th>
<th></th>
<th>K-value</th>
<th>Level of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>RCM rater 2</td>
<td>Negative</td>
<td>101</td>
<td>11</td>
<td>0.751</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>3</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>OCT rater 1</td>
<td>Negative</td>
<td>98</td>
<td>9</td>
<td>0.724</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>7</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>RCM rater 2</td>
<td>Negative</td>
<td>102</td>
<td>3</td>
<td>0.916</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>2</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>OCT rater 2</td>
<td>Negative</td>
<td>100</td>
<td>7</td>
<td>0.653</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>12</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

OCT = optical coherence tomography; RCM reflectance confocal microscopy.

tumor deep margin check in the intra-operative phase by means of ex vivo FCM, on BCC excision.

Our experience disclosed that the combined approach, in vivo OCT/RCM + ex vivo FCM represents a promising new approach to BCC margins identification. Achieving clear narrow margins and attaining the recommended wide safety margins may be complex in some cases, relying only on clinical and dermoscopic criteria. For this reason, we selected a series of BCC showing unclear clinical and dermoscopic margins.

BCC subtypes with aggressive histologic characteristics, poorly defined clinical margins and sites in certain areas, including the H region of the face have been linked to an increased risk of recurrence. For these reasons, Mohs surgery was developed for locally aggressive tumors [18-20].

In cases of poorly defined BCCs, Mohs surgery showed great effectiveness. Primary BCC recurrence rates following routine excision versus MMS are 10% and 1%, respectively. In a randomized trial, the 10-year cumulative probabilities for recurrence in primary BCCs were 12.2% versus 4.4% with standard excision and MMS, respectively [21]. However, the application of Mohs is limited in several healthcare systems due to technological issues, costs and availability of a dedicated pathologist. As a result, several methods have been developed, especially in Europe, to use noninvasive methods to detect lateral tumor margins. In a recent meta-analysis, dermoscopy revealed no statistically significant differences in the proportion of complete margin clearance on the first MMS stage between BCCs treated with dermoscopy-guided MMS and those who underwent curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS [22].

The precise assessment of the dermoscopic margins of infiltrative BCC may be very difficult given that these tumors are often more amelanotic and less heavily pigmented than less aggressive subtypes [23].

In one study, RCM demonstrated good global accuracy for primary BCC lateral margin detection with a sensitivity and specificity of 95%. However, the study has been done only on superficial BCC-type [24]. To note, in our study difficult BCC in terms of clinically definable margins has been included.

OCT displayed a sensitivity of 88.9%-92.6% and a specificity of 96.8%-98.4% on examining BCC-involved margin in 40 BCCs [25]. The major limit of this study is that the histological BCC subtypes were not reported. However, each of these approaches has its limitations. RCM has excellent lateral resolution (~0.1-0.8 μm) but low tissue penetration power (100–200 μm) while OCT has lower lateral resolution (~5-7.5 μm) but higher penetration power (~1mm).

The combined use of RCT and OCT seems to have multiple advantages: OCT displays very quickly (~10 sec/acquisition) the entire volume of the lesion with a stack of orthogonally oriented images, each of FOV 2 mm. OCT imaging detects dark hypoechoic areas, which indicate the potential presence of BCC. RCM confirms OCT data by visualizing BCC features with cellular resolution.

However, none of the non-invasive techniques currently in use enable the vision of deep margin involvement, which is crucial for the possible recurrence of BCC since it might result in infiltration and tumor development in deep tissues.

FCM has been selected for the detection of positive deep margins after surgical excision as RCM and OCT lack to
reach the very deep skin layers. The overall sensitivity and specificity of fluorescence mode FCM for detecting BCC with narrow or incomplete margins were 88.0%–96.6% and 89.2%–99.0% respectively, in a large study performed by Bennassar and colleagues on 80 carcinomas [26]. In more recent devices, reflectance and fluorescence modes may operate simultaneously. The interaction between the two modes increases the identification of BCC features in the fusion mode. The visibility of the tumor and stroma is improved by using acetic acid and acridine orange stains without harming the tissue for further histological investigation [27]. Due to this, we chose to combine RCM and OCT for lateral margin evaluation preoperatively, mutually compensating for each other’s limitations, and to employ FCM intraoperatively for deep margin assessment.

Starting from our study, even if these combined methods are able to determine the exact lateral margins of superficial and nodular BCCs in enface optical sections [28], they both lack to reach the very deep part of the lesions. Adding to the protocol the fast and easy examination with ex vivo FCM of the excised tissue, deep margins can be easily checked with 100% concordance with histology. As the primary endpoint is concerned, the overall positive margins diagnostic accuracy was 98.2% as the agreement between positive margins in RCM/OCT and in histological evaluation (κ = 0.9241). Furthermore, RCM showed a sensitivity of 100% and a specificity of 96.3%, OCT a sensitivity of 96.9% and a specificity of 94.5%. Interestingly, in our study histological examination underlined a high-aggressive BCC subtype unnoticed in dermoscopy in 4 lesions (18.1%). Moreover, in our experience, dermoscopically assisted clinical margin detection was accurate in only 36.4% of cases given the 2mm first step margin from the lesion.

Our study is clearly an employee operator, and our observers’ levels of agreement were generally acceptable. Interobserver evaluation has been made challenging. Neither the clinical nor dermoscopy images were related to the OCT/RCM images.

The investigation, which involved a small number of cases, was conducted in two centers with notable experience in RCM/OCT imaging. The results generalizability must be demonstrated in more patients and across more centers. There is the need of control group for further studies. The complete procedure might be finished in 35-50 minutes with competent hands, but it might take longer with less experienced hands (>40 min).

Potentially, our imaging approach could be extended to intraoperative search for residual cancer [29,30], and postoperative monitoring for local recurrence with the current limit of a not sterilizable HH-RCM probe with the common methods of sterilization used for surgical devices. Integration of RCM/OCT imaging in Mohs surgery could be considered in a presurgical stage potentially able to save time by reducing the required number of Mohs stages.

Line-field confocal optical coherence tomography (LC-OCT) is a novel technique that combines the technological advantages of reflectance confocal microscopy with OCT in a single instrument.

Compared to the procedures used independently, it has a lower resolution, but it allows for a quicker switch between diagnostic techniques, facilitating the diagnosis. However, LC-OCT is unable to provide information on the involvement of the deep margin in non-superficial BCC [31,32].

The information provided by the RCM/OCT/FCM combined procedure has all the potential for routinely applications in the presurgical and intra-surgical assessment of adequate lateral and deep margin in BCC. This procedure is likely to be most beneficial for difficult BCC of particular areas like the face, where wide margins may be difficult to attain.

Moreover, potentially the FCM can be reserved in very deep BCC in which the deep silhouette is not clearly visible when assessed with in-vivo techniques (RCM, OCT, LC-OCT). This approach could potentially lead to a positive impact on the patient’s surgical experience, satisfaction, and improve the physician’s decision-making process. This can decrease patient anxiety, reduce cost by reducing the number of recurrences and improve pre-operative surgical planning by discussing appropriate reconstruction options and potential non-invasive treatment options. In summary, the combined approach RCM/OCT/FCM ex vivo noninvasively facilitates both diagnosis and depth assessment, and consequently BCCs may be treated through a “one-stop shop” approach with no need for a biopsy.

References


26. Bennassar A, Vilata A, Puig S, Malvehy J. Ex vivo fluorescence confocal microscopy for fast evaluation of tumour margins...
Supplementary material

Video S1. FCM procedure showing the specimen preparation, the stain, and the margins exploration in reflectance, fluorescence and combined mode.
Dermoscopy of Actinic Lichen Planus in Skin of Color

Awatef Kelati¹, Asmae Rasso², Soumia Chiheb¹

¹Dermatology Department, University Hospital Cheikh khalifa, and the University Hospital Mohammed VI. Faculty of Medicine, Mohammed VI University of Health and sciences (UM6SS), Casablanca, Morocco
²Dermatology Department, Provincial Hospital of Tantan, Tantan, Morocco

Key words: Dermoscopy, Actinic lichen planus, skin of color, lichen, lichen planus pigmentosus

Citation: Kelati A, Rasso A, Chiheb S. Dermoscopy of Actinic Lichen Planus in Skin of Color. Dermatol Pract Concept. 2024;14(2):e2024101. DOI: https://doi.org/10.5826/dpc.1402a101

Accepted: November 12, 2023; Published: April 2024

Copyright: ©2024 Kelati et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Kelati Awatef, Dermatology Department, University Hospital Cheikh khalifa, and the University Hospital Mohammed VI. Faculty of Medicine, Mohammed VI University of Health and sciences (UM6SS), Casablanca, Morocco. Email: akelati@um6ss.ma

ABSTRACT

Introduction: Actinic Lichen Planus (ALP) is a rare photosensitive variant of lichen planus. Four subtypes can be distinguished: pigmented, annular (AALP), plaque-like and dyschromic ALP.

Methods: This is a retrospective; descriptive and analytical study investigating the dermoscopic patterns of different subtypes of ALP in skin of color.

Results: Sixteen adult patients were included in this study; the majority of them were young females, while five patients with the pigmented subtype of ALP were more than 50 years old. This subtype was more prevalent in patients with phototype IV. AALP was described in men with a very dark phototype.

In pigmented melasma-like ALP, dermoscopy showed an annular granular pattern, white reticular and circular Wickham striae (WS) with hypopigmentation lacking skin creases, dots inside circles and an eccentric pigmentation on circles. In ALP, annular, circular WS; and perifollicular white halos with follicular plugs were described. The black hole pattern with dotted vessels was seen in the dyschromic ALP. White-yellow-bluish WS were noticed in plaque-type ALP with circumferential radial lines at the periphery.

Conclusions: This descriptive study of dermoscopic patterns of various subtypes of ALP in skin of color highlighted new dermoscopic descriptions that vary according to the clinical variant or the morphology; lesions distribution; and phototype. Also, many epidemiological differences were found between our results and the literature concerning the older age of onset in melasma-like pigmented ALP, and the male predominance in annular ALP.
Introduction

Actinic Lichen Planus (ALP) is a rare photosensitive variant of lichen planus (LP); that is known to occur generally in children and young adults of Middle Eastern countries [1]. It was documented using different terms such as lichen planus tropicus, lichen planus subtropicus, summertime actinic lichenoid eruption [2], and lichen planus actinicus [1]. The etiology is still unknown; however, UV radiation appears to be the major incriminated factor, since it occurs primarily during spring and summer, and involves mainly exposed areas of the skin [3]. The hormonal factor was also suggested, especially in melasma-like pigmented forms which are frequent in women [4].

Lesions are usually asymptomatic and involve sun-exposed areas, like the face; especially the forehead, and the extensor surfaces of upper extremities, mainly the dorsum of the hands [5]. Clinically, four subtypes of ALP can be distinguished: pigmented ALP, annular actinic LP (AALP), plaque-like ALP; and dyschromic ALP [5,6].

Pigmented ALP manifests as hyperpigmented (gray, brown, or black) inflammatory macules and patches on sun exposed areas, sometimes giving a melasma-like pattern [4], that worsens after sun exposure. AALP manifests as erythematous brown plaques that are annular in configuration, with central atrophy in some cases [5,7]. In the plaque-like type, the lesions are elevated brown-gray plaques, with a depressed brownish center; and an erythematous elevated border [8]. Dyschromic ALP presents as pinhead-sized, whitish angular infiltrated papules that tend to coalesce, forming lesions of 5 to 6 mm in diameter, with a small horny plug in the center, it is generally described on the posterior part of the neck and the dorsum of the hands [4].

Dermoscopy of LP in the skin of color was not fully investigated, Wickham striae (WS) are more difficult to see in dark phototype. Also, their clinical picture may differ due to variations in morphology and configuration, or clinical features modification depending on the site of involvement [9].

In addition, ALP has not been well described, and existing data of skin imaging in this rare variant of LP concerns only few observations of annular ALP, and pigmented ALP with lack of precisions of dermoscopy in the different variants [1,5,10].

Objectives

The main aim of this study was to describe and analyze dermoscopic patterns of different variants of ALP in skin of color.

Methods

A retrospective double-center descriptive and analytical study was performed in the Dermatology Department of the University Hospital Cheikh khalifa, and the University Hospital Mohammed VI of Casablanca in Morocco, over a period of 3 months, digital dermoscopic images of dark-skinned patients with ALP- were examined and reviewed by two dermatologists experienced in Dermoscopy.

Subjects

Patients with different subtypes of ALP were enrolled in the study. The diagnosis was based on the morphology and the distribution over photo-exposed areas, with a histological confirmation.

Data Analysis

For each patient, epidemiological and clinical data were collected, including the age and the gender, as well as the phototype, lesions location, morphology and distribution.

Dermoscopic images of the representative lesions were taken using a manual dermoscope (HEINE DELTA 30, or DermLite DL 4) attached to a smartphone or a digital camera, with or without polarized light and with or without immersion.

Variables used in the dermoscopic evaluation were WS (presence or absence), type of WS (radial, reticulate, linear, circular, annular, arboriform, perifollicular and mixed), hypopigmentation lacking skin creases, perifollicular hypopigmentation, pigmented structures (diffuse brown pigmentation, blue-gray and brown dots, eccentric pigmentation on circles), follicular plugs, blood vessels (presence or absence and their morphology), background color, particular structures and patterns (annular granular pattern, black hole pattern, pigmented dots arranged in parallel lines, circumferential radial lines).

The annular-granular pattern was considered as multiple, gray dots and globules around the pilo-sebaceous units [11]. The black hole pattern was considered as grayish-white annular and reticular WS at the periphery of the lesions, and clustered brown-gray dots on a light brown background in the center [12].

Data extraction was performed using Excel software (Microsoft). These data were then analyzed using IBM SPSS Statistics version 20 software (IBM), Descriptive statistics were expressed as means and percentages. All subjects were informed of the conditions related to the study and gave their informed consent.

Results

Sixteen patients were included in this study. The mean age was 39.6 +/- 12.8 years (13-55 years); and the majority of patients (7, 43.8%) were young adults (less than 35 years old), while five (31.3%) subjects with pigmented melasma-like subtype had more than 50 years old.
There was a female predominance (75%); with a male-to-female sex ratio of 0.33. All of our patients had dark phototype (IV 10 (62.5%), V 5 (25%); and VI 2 (12.5%)).

Pruritus was absent in most cases, except in the inflammatory areas where an erythema was noted clinically and upon dermoscopy in three patients.

The most predominant clinical subtype in this study was pigmented ALP in twelve patients (75%) with phototype IV, and a melasma-like pattern in most of them, while a pigmented classic-like ALP pattern (papules and patches) was described in one patient. The melasma-like variant affected the full face in seven (63.6%) patients, the forehead in ten (90.9%) patients, the lower part of the face in eight (72.7%) patients, the neck in five (45.4%) patients, and the hands in two patients (18.2%) (Figure 1).

AALP was noticed in two male patients with a very dark phototype (V and VI), body areas involved were the forehead and the dorsal side of the hands (Figure 4). The dyschromic and plaque-like ALP were noticed in one patient each, with the forehead involvement for the plaque subtype, and the hands involvement in the dyschromic subtype.

Hair involvement was described in seven cases (43.7%), with no associated mucous membrane or nail involvement.

In melasma-like pigmented ALP, dermoscopy showed an annular granular pattern, dots inside circles, and eccentric pigmentation on circles in all the cases. Reticular pigmentation in 90.9%; and hypopigmentation lacking skin creases surrounded by diffuse peppering was described in 81.8% of cases. Peri-follicular hypopigmentation was found in 45.5% of patients, white reticular and arborescent WS surrounded by pigmented areas and brown to gray dots were described in 18.2% of cases.

In AALP and plaque-like ALP, annular and circular white WS surrounded by pigmented areas were described, in addition to reticular pigmentation, follicular plugs, white halo around follicular openings; pigmented dots arranged in parallel lines; and circumferential radial lines at the periphery of some annular plaques.

Figure 1. Pigmented Actinic Lichen Planus. Hyperpigmented (gray brown) macules and patches on sun exposed areas in a melasma-like pattern, that worsen after sun exposure.
ALP is a rare variant of this disease with a seasonal occurrence, a predilection for dark-skinned females, an earlier age of onset; and a longer course [8].

In this study, we have found that this disease did not affect only children and young female adults as it was reported in the literature [5,6], it was also noticed in older patients; especially for the pigmented melasma-like subtype, this was also reported in a clinicopathological study of ALP and lichen planus pigmentosus, with a female to male ratio of 1.74, and a mean age of patients of 48.02±14.83 [13], however; this study did not describe and focus on the different subtypes of ALP, and also dermoscopy was not reported.

The pigmented melasma-like subtype was the most predominant in our study, unlike data reported in the literature, that the most frequently presenting form is the AALP [6,14], this pigmented subtype was known to occur mostly in women [15], which joined our results. However, our patients with AALP were men with a very dark phototype.

White-yellow-bluish WS were noticed in one patient with a very dark phototype and annular plaques on the dorsum of the hands.

The black hole pattern was described in the patient with dyschromic ALP of the hands, with dotted vessels on the white annular WS in a radial linear distribution (Figures 2-10).

Histological confirmation reveals findings similar to those of classic LP with degeneration of the basal layer of the epidermis; a band-like lymphocytic infiltrate of the dermis obscuring the dermo-epidermal junction, with pigmentary incontinence, and follicular involvement in some cases.

Conclusions

There are many variants of lichen planus, the morphology and distribution differ largely depending on its clinical and histological subtype [5].

ALP is a rare variant of this disease with a seasonal occurrence, a predilection for dark-skinned females, an earlier age of onset; and a longer course [8].

In this study, we have found that this disease did not affect only children and young female adults as it was reported in the literature [5,6], it was also noticed in older patients; especially for the pigmented melasma-like subtype, this was also reported in a clinicopathological study of ALP and lichen planus pigmentosus, with a female to male ratio of 1.74, and a mean age of patients of 48.02±14.83 [13], however; this study did not describe and focus on the different subtypes of ALP, and also dermoscopy was not reported.

The pigmented melasma-like subtype was the most predominant in our study, unlike data reported in the literature, that the most frequently presenting form is the AALP [6,14], this pigmented subtype was known to occur mostly in women [15], which joined our results. However, our patients with AALP were men with a very dark phototype.

**Figure 2.** Dermoscopy of pigmented melasma-like Actinic Lichen Planus. Annular granular pattern (green circle) with reticular pigmentation, white linear and reticular Wickham striae (C and D, blue arrow), surrounded by pigmented areas and dots. Dots inside circles (blue circle) and eccentric pigmentation on circles (blue rectangle) in some areas.
**Figure 3.** Dermoscopy of pigmented melasma-like Actinic Lichen Planus. Annular granular pattern with reticular pigmentation, hypopigmentation lacking skin creases (blue arrow), surrounded by brow-gray dots. Dots inside circles (blue circle) and an eccentric pigmentation on circles (blue rectangle), with an erythematous background (red star).

**Figure 4:** Annular Actinic Lichen Planus. Pigmented annular plaques on the forehead and the dorsum of the hands in two dark-skinned patients.
In various subtypes of LP, WS have been reported to be structured white areas that correlate with an increase in the granular cell layer in the epidermis, or a focal increase in the epidermal activity and irregular acanthosis leading to striae formation. Blood vessels were especially noticed in fair phototype around WS with a lack of dermal vessels in the striae area [9], due to epidermal proliferation that decreases their visualization [16]. However in pigmented forms of LP, especially macular lesions, and in very dark phototypes, WS can be difficult to see, can have various forms, or can be unapparent. Hypopigmentation lacking skin creases surrounded by pigmented dots and areas was a frequent finding in the pigmented melasma-like subtype in our study. Annular configuration of ALP was particularly reported [12,17], with a white-bluish coloration of WS [17], which was also noticed in our study in AALP and plaque-like ALP. Pigmented dots
Figure 7. Annular Actinic Lichen Planus (A) Before treatment: white halo around follicular openings (blue arrow); and Wickham striae (green arrow). (B) After treatment: disappearance of these dermoscopic signs, with persistence of pigmented structures (pigmented areas, and dots) (red arrow).

Figure 8. Plaque-like Actinic Lichen Planus. (A) Confluent brown-gray plaques on the forehead with a depressed brownish center in some spots (8). (B) Dyschromic Actinic Lichen Planus. Pinhead-sized, whitish confluent papules, with a small horny plug in the center, on the dorsum of the hands.

In the active stage of LP, many dermoscopic findings could be found, mainly WS surrounded by dotted or lineal vessels enhancing their visualization, and erythema. In dark skin, WS are the main structures described in active lesions with an absence of vascular structures [17], except for the dyschromic ALP, as we reported in our study, where we can find dotted vessels in a linear and a radial distribution on annular WS. Erythema could be noticed especially in phototype IV, and may correlate with the presence of symptoms, like pruritus as we noticed in three of our patients with ALP.

On the other hand, in the resolution phase, WS are absent, with fine or coarse gray-blue, brown or brown-black dots on a brown background [5,16]. WS are therefore a good marker of therapeutic efficiency that disappears with
International Dermoscopy Society reported dermoscopy of the pigmented form of lichen actinicus with the main dermoscopic feature as periosteal brown dots and brown structure-less areas with ostial sparing [10].

This descriptive study of dermoscopic patterns of various subtypes of ALP highlighted new dermoscopic descriptions that vary according to the clinical variant or the morphology, lesions distribution, and the phototype. Also, some epidemiological differences were noticed in comparison with the previous publications, concerning the older age of onset in melasma-like pigmented ALP, and the male predominance in annular ALP. Other prospective studies with a large number

treatment. Pigmented structures could however resist treatment, which was also noticed in our ALP patients (Figure 7).

Dermoscopic particularities of ALP were not fully described and investigated, only three publications [1,5] exist in the literature (Table 1). One concerned the annular variant of ALP, another reported a case of macular ALP that was misdiagnosed as lentigo maligna, due to the overlapping dermoscopic patterns found in the two diagnoses, especially the melasma-like ALP, such as diffuse peppering, hyperpigmented follicular openings, signet ring-like sign, and circles with central black dots [1], and an interesting study of non-neoplastic dermatoses in skin of colour by the

**Figure 9.** Plaque-like Actinic Lichen Planus dermoscopy: follicular white halo (red circle) surrounded by a pigmented rim, and pigmented dots arranged in parallel lines (blue arrow). In less elevated areas, we notice dots inside circles (blue circle), eccentric pigmentation on circles (blue rectangle), and circumferential radial lines at the periphery of the plaques (blue star).

**Figure 10.** Dyschromic Actinic Lichen Planus on the dorsum of the hands. Black hole pattern (blue circle) with annular Wickham striae and brown-grayish globules in the center. Central follicular plugs in some of the lesions (blue arrow), and dotted vessels with a radial linear distribution on the Wickham striae (red arrow).
Table 1. Dermatoscopic differences between Actinic Lichen Planus and classic Lichen Planus with a dermoscopy pathology correlation

<table>
<thead>
<tr>
<th>Dermoscopic signs</th>
<th>Classic lichen planus</th>
<th>Actinic lichen planus</th>
<th>Dermatopathologic correlations of dermoscopic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wickham striae (18)</td>
<td>Polymorphic pearly white structures (rounded, arboriform, reticular, annular), Blue-white</td>
<td>White circular and reticular</td>
<td>Hypergranulosis with acanthosis</td>
</tr>
<tr>
<td>• Dark phototype (19,20)</td>
<td>Polymorphic pearly white structures (rounded, arboriform, reticular, annular), Blue-white</td>
<td>White-yellow-bluish WS</td>
<td></td>
</tr>
<tr>
<td>Pigmented structures</td>
<td>Active lesions</td>
<td>Active ad late lesions</td>
<td>Melanin incontinence</td>
</tr>
<tr>
<td>Annular granular pattern</td>
<td>Not described</td>
<td>Pigmented melasma-like ALP</td>
<td>Melanin incontinence</td>
</tr>
<tr>
<td>Dots inside circles</td>
<td>Not described</td>
<td>Pigmented melasma-like ALP</td>
<td>Melanin incontinence</td>
</tr>
<tr>
<td>Eccentric pigmentation on circles</td>
<td>Not described</td>
<td>Pigmented melasma-like ALP</td>
<td>Melanin incontinence</td>
</tr>
<tr>
<td>Blue-gray granules</td>
<td>Yes</td>
<td>Pigmented melasma-like ALP</td>
<td>Melanin incontinence</td>
</tr>
<tr>
<td>Periosteal brown dots and brown structureless areas with ostial sparing (10)</td>
<td>Not described</td>
<td>Pigmented ALP</td>
<td></td>
</tr>
<tr>
<td>Hypopigmentation lacking skin creases</td>
<td>Not described</td>
<td>Pigmented melasma-like ALP</td>
<td>Irregular acanthosis. and hypergranulosis</td>
</tr>
<tr>
<td>Perifollicular white halos</td>
<td>Not described</td>
<td>AALP and plaque-like ALP</td>
<td>Early perifollicular fibrosis</td>
</tr>
<tr>
<td>Follicular plugs</td>
<td>Hypertrophic forms of LP</td>
<td>AALP and plaque-like ALP</td>
<td>Follicular hyperkeratosis</td>
</tr>
<tr>
<td>White scales</td>
<td>Yes, may be diffuse obscuring the visibility of shiny white structures and Wickham striae</td>
<td>Fine scales</td>
<td>Orthokeratosis</td>
</tr>
<tr>
<td>Shiny white structures (19)</td>
<td>Reticular lines, and structurless areas</td>
<td>Reticular lines and perifollicular in AALP and plaque-like ALP</td>
<td>Dermal fibrosis</td>
</tr>
<tr>
<td>Circumferential radial lines at the periphery</td>
<td>Not described</td>
<td>AALP and plaque-like ALP</td>
<td>Peripheral extension of the basal vacuolization, the dermal inflammatory infiltrate and the pigmentary incontinence</td>
</tr>
<tr>
<td>Pigmented dots arranged in parallel lines</td>
<td>Not described</td>
<td>AALP and plaque-like ALP</td>
<td>Melanin incontinence</td>
</tr>
<tr>
<td>Vascular structures</td>
<td>Radial capillaries with dotted, globular and/or linear vessels, mainly localized at the periphery of the lesion (and less commonly showing a perifollicular or a diffuse pattern) (21)</td>
<td>Dotted vessels in Dyschromic ALP</td>
<td>Dermal vessels</td>
</tr>
<tr>
<td>Background</td>
<td>Pink violet, reddish and blue–gray, brown or yellow background</td>
<td>Light to dark brown violaceous blue–gray background</td>
<td></td>
</tr>
</tbody>
</table>

ALP = Actinic Lichen Planus; AALP = annular Actinic Lichen Planus; LP = Lichen Planus.
of patients are warranted in order to fill the gap in the literature concerning dermoscopy of ALP and other variants of LP especially in dark phototype.

References


Dermatitis Artefacta: A Retrospective Descriptive Study on 46 Patients

Eugenia Veronica Di Brizzi¹, Gianluca Ficca², Vincenzo Piccolo¹, Camila Scharf¹, Giulia Briatico¹, Sebastiano Pellerone¹, Giuseppe Argenziano¹

¹ Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy
² Department of Psychology, University of Campania Luigi Vanvitelli, Naples, Italy

Key words: artefact dermatitis, patomimia, self-induced dermatoses, dermatology


Accepted: November 2, 2023; Published: April 2024

Copyright: ©2024 Di Brizzi et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
Corresponding Author: Eugenia Veronica Di Brizzi, MD, Dermatology Unit, University of Campania, Nuovo Policlinico (edificio 9C), Via Pansini 5, 80131 Naples Italy. E-mail: eugeniaveronica.dibrizzi@gmail.com

ABSTRACT

Introduction: Self-induced dermatoses are self-inflicted skin lesions, whose occurrence patient denies responsibility for.

Objectives: The aim of this study was to retrospectively investigate all the clinical records of dermatitis artefacta (DA) in order to put special focus on: a) epidemiological aspects; b) location, shape and additional features of the lesions; c) availability of psychiatric details in the records.

Methods: A retrospective observational descriptive study on 46 patients affected by dermatitis artefacta was conducted from January 2015 to March 2021. The only inclusion criterion was clinical or histological diagnosis of DA in patients for which we had clinical images.

Results: The most frequent type of lesions were erosions/excoriations and ulcers (14/46, 30.4% and 13/46, 28.3% respectively) followed by ecchymoses (9/46, 19.5%), vasculitis-like lesions (3/46, 10.9%), crusted plaques (3/46, 6.5%), scales (1/46, 2.2%) and erythema (1/46, 2.2%). Thirty-three percent of the medical records generically referred to the presence of psychiatric disorder, but none of them included a specific psychiatric diagnosis.

Conclusions: In our study the main dermatologic lesions observed in DA were represented by excoriations and ulcers and that the shape and location of the lesions are essential for a correct diagnosis.
Introduction

Self-induced dermatoses are self-inflicted skin lesions, whose occurrence patient denies responsibility for. Although self-induced dermatoses in the general population are underdiagnosed, making it difficult to ascertain their correct prevalence, they account for about 2% of the requests for dermatological consultation [1,2].

They are three-five times more frequent in women than in men, with greater prevalence in those with lower socio-economic status, and can occur at any age, with a higher frequency in early adulthood [3,4].

Similar epidemiological evidence is to be observed for dermatitis artefacta (DA), also known as patomimia), characterized by the induction of injuries or diseases in order to satisfy a conscious or unconscious desire to assume the sick role in the absence of external awards (unlike the malingering, in which skin damage may be inflicted for the purpose of secondary gain) [5,6].

In fact, DA is usually underdiagnosed due to diagnostic difficulty, which is probably why there are so few published series of DA [4-7,8]. A retrospective study of 57 patients reported a 2.8 higher prevalence in females than in males, with multiple lesions in 88% of patients: of these 57 patients, only 18% had a psychiatric diagnosis [4]. An epidemiological study conducted in Iran on 178 patients reported that anxiety disorders were common in these patients [7]. Most studies are limited to clinical cases that have aroused the clinician interest for their peculiar clinical expression.

DA etiopathogenesis is multifactorial and, interestingly, there is a major psychiatric component. Indeed, an association has been found between self-induced dermatoses and psychiatric disorders including depression, borderline personality disorder and post-traumatic stress disorder (PTSD) [9]. Moreover, onset of DA is often preceded by psychosocial stress especially during early development (eg loss of a parent, parental divorce and/or mistreatment) [10]. Therefore, it does not surprise that DA is duly considered in the current psychiatric nosology, being included in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) among the fictitious disorders. In other terms, just like in Münchhausen syndrome, patients create artefactual lesions or a disease to gain both hospital admission and the attention associated with having a difficult-to-identify condition [11,12].

Clinical appearance of DA depends on the method used for self-injuries. Excoriations and ulcers, dermatitis-like lesions, panniculitis, ecchymosis, and vasculitis-like lesions are all possible [13].

Sometimes the lesions show bizarre and obviously artificial aspect, surrounded by non-injured skin; however, they can mimic any disorder including pyoderma gangrenosum, intertriginous and flexural erythema, and ulcers, resembling rare tumors [14-19].

Injuries might be produced by scratching, picking, biting, cutting, heat, ice cold or boiling water, and injectable chemicals. Lesions can have bizarre shape and distribution, with geometric, linear edges, clearly delimited by healthy skin, being quite frequently seen (Figures 1 and 2).

The diagnosis is difficult due a wide variety of possible differential diagnoses. The diversity of the means and the methods used by the patient to injure him/herself should be taken into consideration, together with the morphology of the lesions and the history [20]. Complications such as gangrene, abscess formation, or other life-threatening infections are also possible. Several anatomic sites may be involved, but they are usually confined to areas within easy reach [3]. The patients typical lack of concern for how disfiguring their lesions appear is amazingly disproportional relative to the entity of their presentation. The patient history does not tend to corroborate the unusual cutaneous findings.

Objectives

The aim of this study was to retrospectively investigate all the clinical records of DA available at our Dermatological Unit, sampled over around six years, in order to put special focus on: a) epidemiological aspects; b) location, shape and additional features of the lesions, to better understand which of them could be pivotal for making a correct diagnosis; c) availability of psychiatric details in the records, given the above-mentioned connections of DA with psychopathology.

Methods

A retrospective observational descriptive study on 46 patients affected by DA was conducted at the Dermatology Unit of the University of Campania “Luigi Vanvitelli” from
January 2015 to March 2021. The only inclusion criterion was clinical or histological diagnosis of DA in patients for which we had clinical images. Patients suffering from concomitant inflammatory skin diseases were excluded from the study. The main clinical criteria considered for the diagnosis of DA were the presence of lesions with a regular and geometric appearance, a characteristic morphology that suggests the means used to self-mutilate, involvement of body sites easily reachable by the hands and localization of the lesions on the non-dominant side of the body. Regarding histological criteria the main characteristics considered were epidermal necrosis with modest inflammatory process in the dermis, vesico-bullous lesions with full thickness epidermal necrosis, clear margins and poor inflammatory infiltrate without eosinophils, the presence of skin material – dermal or subcutaneous foreign body granuloma. The following parameters were recorded for each patient: age, sex, type of lesion (excoriation, ulceration, erythema, patch, blister, desquamation, hyperpigmentation, vesicle, plaque, crust), site of the lesion (head/neck, upper and lower limbs, trunk, buttocks, acral regions or widespread), distribution of the lesion (random or with specific pattern, symmetrical or asymmetrical) and number of lesions (single or multiple). A histopathologic examination was performed in 23 patients (Table 1). Each participant gave written informed consent form.

Table 1. Patients features and location of lesions (N = 46).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>• M</td>
<td>24 (52)</td>
</tr>
<tr>
<td>• F</td>
<td>22 (48)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>40</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>• Widespread</td>
<td>13 (28)</td>
</tr>
<tr>
<td>• Head/neck</td>
<td>10 (22)</td>
</tr>
<tr>
<td>• Lower limbs</td>
<td>8 (17)</td>
</tr>
<tr>
<td>• Upper limbs</td>
<td>6 (13)</td>
</tr>
<tr>
<td>• Trunk</td>
<td>4 (9)</td>
</tr>
<tr>
<td>• Acral</td>
<td>3 (7)</td>
</tr>
<tr>
<td>• Buttocks</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Figure 2. (A) Erythematous lesions localized on the face and clavicular region of a woman. (B) Self-induced excoriations localized on the forehead. (C) Self-induced ulcer localized on the right leg. (D). Ecchymotic lesions of the left leg.
Results

Images of DA belonging to 46 patients were evaluated. 24 patients were males (52%) and 22 females (48%) aged between 3 to 87 years (mean + SD = 40 + 24.5). The most frequent lesions distribution was widespread (13/46, 28%), followed by the head/neck area (10/46, 22%), lower limbs (8/46, 17%), upper limbs (6/46, 13%), trunk (4/46, 9%), acral region (3/46, 7%) and buttocks (2/46, 4%) (Table 1).

Lesions showed a regular and geometric appearance in 40% of patients and often the morphology was enough to suggest the means used to self-mutilate. In 20% of cases the injuries involved the side of the non-dominant body site.

All lesions were located on parts of the body easily reachable by the hands.

The most frequent type of lesions were erosions/excoriations and ulcers (14/46, 30.4% and 13/46, 28.3% respectively) followed by ecchymoses (9/46, 19.5%), vasculitis-like lesions (5/46, 10.9%), crusted plaques (3/46, 6.5%), scales (1/46, 2.2%) and erythema (1/46, 2.2%) (Table 2).

We also calculated the associations between different types of lesions and the affected anatomical sites. As regards the most frequent lesions the erosions/excoriations were localized most frequently in the head-neck area (38%) followed by localization in the upper and lower limbs (23% respectively) and finally in the trunk and buttocks (8% respectively); the ulcers had a mainly widespread distribution and in the head-neck area (36% respectively) followed by the buttocks and lower limbs (14% respectively) (Table 3).

Regarding the 23 cases subjected to biopsy and histological examination, most frequent type of lesions were erosions/excoriations and ulcers (8/23, 34.8% and 9/23, 39.1% respectively) followed by vasculitis-like lesions (4/23, 17.4%), crusted plaques (1/23, 4.3%), erythema (1/23, 4.3%) and ecchymosis (1/23, 4.3%).

Thirty-three % of the medical records generically referred to the presence of psychiatric symptoms (such as, for instance, altered mood, atypical behaviors, socio-relational difficulties), but none of them included a specific psychiatric diagnosis made according to conventional taxonomy.

Conclusions

Findings of this study may provide further evidence to the understanding of both the epidemiology and the phenomenology of DA. This disorder usually affects women more frequently, while in our study the M/F ratio was comparable [21]. Most frequently lesions were widespread or located in the head/neck area. Consistently with the data reported in the literature, erosions/excoriations and ulcers were the most frequent lesions, suggesting that this aspect could be an important clue for the correct diagnosis [22,23].

Histopathologic examination was performed in 23 cases, in which the patient presented lesions with clinical elements suggesting other skin conditions. The biopsy excluded the presence of specific elements of other diseases and therefore allowed, together with other anamnestic and clinical features, to perform a diagnosis of DA.

Lesions showed a regular and geometric appearance in 40% of patients and often the morphology was enough to suggest the means used to self-mutilate. In 20% of cases the injuries involved the side of the non-dominant body site. The following represent common characteristics in DA. We found that most ulcerated lesions and excoriation/erosions

Table 2. Clinical features of dermatitis artefacta.

<table>
<thead>
<tr>
<th>Type of lesions</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions/excoriations</td>
<td>14 (30.4)</td>
</tr>
<tr>
<td>Ulcers</td>
<td>13 (28.3)</td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>9 (19.5)</td>
</tr>
<tr>
<td>Vasculitis-like lesions</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Crusted plaques</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Scales</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

Table 3. Associations between the different types of lesions and the anatomical sites.

<table>
<thead>
<tr>
<th>Type of lesions</th>
<th>Widespread (%)</th>
<th>Head/neck (%)</th>
<th>Lower limbs (%)</th>
<th>Upper limbs (%)</th>
<th>Trunk (%)</th>
<th>Acral (%)</th>
<th>Buttocks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions/excoriations</td>
<td>38</td>
<td>23</td>
<td>23</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Ulcers</td>
<td>36</td>
<td>36</td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecchymoses</td>
<td>44</td>
<td>22</td>
<td>22%</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis-like lesions</td>
<td>60</td>
<td></td>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crusted plaques</td>
<td>33</td>
<td>33</td>
<td></td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
were caused by manipulation with the nails; most eczematoses were caused by the sucking mechanism and that the vasculitis-like lesions were caused mainly by burning means.

Interestingly, no specific psychiatric diagnosis was reported in any medical records, highlighting how much this relevant aspect is usually underestimated. In our view, this appears to be a very critical point, since a full psychiatric evaluation is definitely required to clarify the diagnosis and to define the correct therapeutic intervention. Therefore, a clinical multidisciplinary approach, including also psychological and psychiatric assessments in the first place, would be recommendable to cope with this problem.

In conclusion, in our study the main dermatologic lesions observed in DA were represented by excoriations and ulcers and that the shape and location of the lesions are essential for a correct diagnosis. Further study is needed specially to clarify the psychological and/or psychiatric background associated to DA to improve the management of such a difficult to diagnose and to treat disorder.

References


Correlation of Specific Inflammatory Markers With the Occurrence of Depression in Patients With Psoriasis and Their Use as Biomarkers for the Diagnosis of Depression

Eleni Mitsiou1, Aikaterini Kyriakou1, Eleni Parlapani2, Anastasia Trigoni1, Myrto Trakatelli1, Zoe Apalla1, Dimitrios Sotiriadis1, Elizabeth Lazaridou1, Aikaterini Patsatsi1

1 2nd Dermatology Department, Aristotle University School of Medicine, Papageorgiou Hospital, Thessaloniki, Greece
2 1st Department of Psychiatry, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Key words: psoriasis, depression, inflammation, CRP, ESR

Citation: Mitsiou E, Kyriakou A, Parlapani E, et al. Correlation of Specific Inflammatory Markers With the Occurrence of Depression in Patients With Psoriasis and Their Use as Biomarkers for the Diagnosis Of Depression. Dermatol Pract Concept. 2024;14(2):e2024104. DOI: https://doi.org/10.5826/dpc.1402a104

Accepted: December 12, 2023; Published: April 2024

Copyright: ©2024 Mitsiou et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Eleni Mitsiou, 2nd Dermatology Department, Aristotle University School of Medicine, Elias 6, GR-59132, Veroia (Greece), Tel. +30 6973032982, E-Mail: mitsiou_elena@yahoo.gr

ABSTRACT

Introduction: Psoriasis is a systemic disease of the skin and nails associated with a wide range of comorbidities such as depression, psoriatic arthritis and metabolic syndrome.

Objectives: The study aimed to examine a potential association between inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and depression in patients with psoriasis.

Methods: A total of 80 individuals were enrolled in the study. Case participants included 28 patients diagnosed with Psoriasis (Beck Depression Inventory-II: 0-13) and 24 patients diagnosed with Psoriasis and Depression (Beck Depression Inventory-II:14-63). Twenty-eight (28) healthy participants comprised the control group.

Psoriasis severity was evaluated by using Psoriasis Area and Severity Index, Physician Global Assessment, Body Surface Area and Dermatology Life Quality Index. Written approval was obtained for its use in this study: Cardiff University (09/2015). Other factors considered in the study were obesity using the Body Mass Index, the levels of stress using the Beck Anxiety Inventory, and the presence of insomnia using the Athens Insomnia Scale. Blood draws and inflammatory markers measurements were performed for all participants.
Introduction

According to the World Health Organization, psoriasis is defined as “a chronic, non-communicable, painful, disfiguring and disabling disease for which there is no cure and with great negative impact on patients quality of life (QoL). Psoriasis involves the skin and nails and is associated with a number of comorbidities. [1]”.

The etiology of psoriasis is complex and has not yet been fully elucidated. In patients with genetic predisposition, inflammation initiation is triggered by an exogenous or endogenous stimulus, leading to the appearance of psoriatic plaque. Several evidence underline the interaction between host genetics and environmental factors in stimulating T-cell-mediated inflammatory processes against self-antigens in psoriasis [2]. Various other cells including dermal dendritic cells, keratinocytes and neutrophils are involved in the immunopathology of psoriasis. The interplay between these cells creates the development of a self-sustained cycle of inflammation around the IL-23/IL-17 axis.

Lately, research has been focused on the role of Tissue Resident Memory (TRM) T-cells in the course of lesions formation in psoriasis. TRM T-cells, a subset of T-memory cells, appear to produce the proinflammatory cytokines IL-17, interferon-γ and IL-22. Interestingly, even after the remission of psoriatic lesions following treatment, inflammation remains in the apparently healthy tissue in the form of resident TRM cells, as trace of immunological memory [3].

Depression in psoriasis has a substantial effect on the quality of everyday life and the emotional state of patients with psoriasis [4,5].

The association of psoriasis with sleep deprivation, nervousness, and inability to relax have also been shown to negatively affect concentration and daily performance [6,7].

Psoriasis patients are often stigmatized in their daily lives by their visible lesions, which negatively affects their mental health state, causing anxiety and depression [8-11]. The severity of the depressive symptoms is not proportional to the severity of the disease. Psoriasis can be mild, even a small spot may affect the mental sphere of the person with psoriasis [12]. It seems that the onset of depression is more common in women compared to men and in those younger than 31 years [13].

Overall, depression, which very often accompanies psoriasis, is characterized by depressed mood, anhedonia and loss of interest, social withdrawal, sleep, and appetite disturbances. Many times, patients suffering from psoriasis are possessed by feelings of shame, not feeling comfortable in their interpersonal relationships, and do not want to be touched (sexual dysfunction often coexists). There is a mutual relationship between psoriasis and depression, patients with psoriasis show a higher degree of depression than healthy people, and patients with depression show more psoriasis [14].

Although still relatively unknown, it has been postulated that psoriasis in younger adults may have even greater psychological impact as they are more prone to addictive behaviors, such as alcohol, experience loneliness, stigmatization, and low self-esteem, while, suicidal ideations are also more intense, COVID-19 – related stress as well as the continued economic pressure experienced by humanity in the recent years have triggered the occurrence of psoriasis and have greatly increased the incidence of disease relapses, and depressive illness. [15-17].

The immunological background in the pathophysiology of depression has been illustrated by several studies. Furthermore, it has been shown that there are common pathogenetic mechanisms in psoriasis and depression. These two facts can justify the occurrence of increased pro-inflammatory cytokines such as C-reactive protein (CRP), TNF-α, IL-17, and IL-6 in both diseases [18-26] while the brain barrier has been shown to be affected, as well. Stress may also play a role in the exacerbation of psoriasis, by dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic–adrenal–medullary axis, peripheral nervous system, and immune system [27]. Stress-related increased cortisol levels (due to increased ACTH production) have also been associated with psoriasis exacerbation [28]. An important role in the appearance of depression on Brain skin axis, has been shown [28] with the release of the ACTH hormone and the release of inflammatory factors: IFN-α, IL-2, IL-6, IL-1β and TNF-α.

Methods

Participants

All participants were recruited from the Psoriasis Outpatient Clinic of the 2nd Department of Dermatology and Venereology, Aristotle University of Thessaloniki.

The study was approved by the Scientific Committee of Papageorgiou General Hospital after permission from the
Hellenic Data Protection Authority. All the participants were thoroughly informed about the scope of the study and were provided with written informed consent, without receiving any financial benefits.

A total number of 52 patients (ie, case participants) was enrolled in the study of whom 28 were diagnosed with Psoriasis (Beck Depression Inventory-II: 0-13), and 24 were diagnosed with Psoriasis and Depression (Beck Depression Inventory-II:14-63). Twenty-eight (28) controls (ie, healthy participants) were also included in the study. The final diagnosis of depression was made by a psychiatrist. As a result, two of our patients with psoriasis and depression were excluded from the second blood sampling because they needed to receive systemic antidepressant treatment.

Blood samples were taken from all participants for the identification and measurement of CRP and erythrocyte sedimentation rate (ESR), as markers of inflammation.

The following inclusion criteria were applied: (a) The patient suffers from moderate to severe psoriasis (body surface area [BSA] > 10 or Psoriasis Area and Severity Index [PASI] > 10 and Dermatology Life Quality Index [DLQI] > 10). (b) The patient suffers from moderate to severe depression. (c) The patient should not follow systemic treatment for psoriasis or for depression, the period stopped for the respective treatment should not be shorter than the period calculated according to the formula: t1/2 (half-life time of the drug he was taking x 5, according to drugs SPC (summary of product characteristics) [68]). (e) Initiation after admission to study systemic therapy for psoriasis. (f) Greek as a native language. (g) Healthy at the time/ not fever / not infection.

Specific conditions that were considered as exclusion criteria were: (a) Adults over 65 years of age. (b) Under 18 years of age. (c) Pregnancy/breastfeeding. (d) Mild psoriasis: BSA ≤ 10, PASI ≤ 10 and DLQI ≤ 10 [19]. (e) Diagnosed psoriatic arthritis. (f) Coexistence of another autoimmune disease. (g) Immunosuppression. (h) Malignancy. (i) PUVA. (j) Patients with Palmoplantar psoriasis. (k) Patients with Pustular psoriasis. (l) Patients with Palmarpsoriasis. (m) Patients receiving systemic treatment for psoriasis or depression over a shorter period calculated according to the formula: t1/2 (drug half-life) x 5 according to drugs SPC (summary of product characteristics) [68]. (n) Psychiatric disorders other than depression included substance dependence disorder. (o) Fever or any type of infection. (p) Crohn disease (q) Anemia.

**Time Points Selection**

a. For healthy controls (i) Day 0: taking informed consents and history of the patient, filling out questionnaires, and blood sampling for the measurement of CRP, ESR.

b. For Patients with Psoriasis and Depression and Patients with Psoriasis: (i) Day 0: taking informed consents and history of the patient, filling out questionnaires, blood sampling for the measurement of CRP and ESR, initiation of systemic treatment for psoriasis (ii) 3 months later since Day 0 and if the same systemic treatment for psoriasis continues: history taking, filling out questionnaires, blood sampling for the measurement of CRP and ESR.

**Psoriasis Assessment Tools/Methods**

**Psoriasis Area Severity Index (PASI)** [29,30]

**Physician Global Assessment (PGA)**: PGA score is a physician-reported measure of psoriasis severity, using a 6-point measure. Lower PGA scores indicate a better skin condition [31,32].

**Body Surface Area (BSA)**: The palming method is used for the calculation, considering that one palm of the hand is about 1% of the body surface [33,34].

**Dermatology Life Quality Index (DLQI)**: All questions refer to the last week before the exam. Higher DLQI scores indicate lower quality of life [35].

**Beck Depression Inventory-II (BDI-II)**: a 21-item self-report instrument, measuring different aspects of depression on a 4-point severity scale during the last two weeks [36,37].

**Body Mass Index (BMI)**: It is calculated based on the formula: BMI = weight(kg)/height² (m²) and determines the ideal weight of each person based on height and kilograms . Recent data lead to the conclusion that obesity is not just epidemiologically related as a comorbidity with psoriasis but is a causative risk factor for the onset or worsening of psoriasis. Obesity is therefore related to psoriasis with common inflammatory factors while it is mainly characterized by increased leptin, resistin, and chemerin but also decreased adiponectin (adipocytokines) [38,39].

**Athens Insomnia Scale (AIS)**: The Athens Insomnia Scale is an effective and easy sleep analysis tool. There are studies that report that inflammation markers are affected by sleep quality [40,41,42,7,].

**Beck Anxiety Inventory (BAI)**: It is a self-report assessment for measuring various stress symptoms by patients during the last week since completing the questionnaire (ie, Day 0). If the symptoms persist, the help of a mental health specialist may be needed [43].

**Inflammation Markers**

**CRP**

CRP belongs to the acute phase proteins and its levels increase in the serum immediately after the onset of the inflammatory reaction. It is produced exclusively in the liver and exhibits both pro-inflammatory and anti-inflammatory properties and plays a role in the non-specific response.
ESR
ESR is the rate at which red blood cells settle in the plasma and is expressed in mm per hour.
It is classified in blood tests. No special procedures are required before blood sampling. For blood, the collection is
used special closed tubes of vacuum air with sodium citrate (sodium citrate 3.2%), usually black in color. The Westergren method measures the distance in millimeters (mm) that red blood cells in anticoagulated whole blood fall to the bottom of a standard upright, elongated tube (Westergren tube) over the course of one hour because of gravity [45]. The normal value varies between 10 and 15 mm in the first hour (for women 12-20 mm). The ESR test is not specific for any disease but is used in conjunction with other tests to identify increased inflammatory activity.

Statistical Analysis
Baseline differences in ESR and CRP levels among groups were analyzed using regression models and adjusting for BMI values. Multiple comparison tests were applied to determine statistically significant pairwise differences based on Bonferroni adjusted p-values. Repeated measures general linear models were applied to examine the differences between the two-time points and between the two groups of patients regarding CRP and ESR levels. The changes were adjusted for baseline values of BMI, PASI score, BGA score, BSA score, DLQI score, BAI score, AIS score, age, gender, and treatment. Statistical significance was set at 0.05 and the analysis was carried out using STATISTICA v 12.0.

Results
Characteristics of Participants
Their baseline characteristics appear in table 1 and other epidemiological characteristics in Table 1 below.
Other Clinical Characteristics of individuals enrolled in the study appears in Table 2 based on a semi-structured interview and patients' medical records.
The study examines the difference observed in CRP and ESR values among the three groups at baseline, as well as the changes observed within a period of three months in the two groups. (psoriasis, psoriasis and depression). Regarding differences at baseline and ESR, statistically significant differences were observed between groups ($F_{2,76} = 6.312 \ P = 0.03$), after adjusting for baseline BMI values. Specifically, patients suffering from Psoriasis and Depression showed higher levels of ESR than patients diagnosed with Psoriasis but no depression ($P = 0.032$). The difference between patients suffering Psoriasis and Depression vs controls was also statistically significant as the adjusted p value for multiple comparisons was found to be 0.022. No differences were observed between patients with Psoriasis and controls ($P = 1.000$). The distribution of data is displayed by a boxplot-type of diagram in Figure 1.
Regarding CRP measurements at baseline, statistically significant differences were observed between healthy controls and both groups of patients suffering from Psoriasis, with or without depression ($F_{2,76} = 6.937 \ P = 0.002$). Specifically, higher CRP levels were observed in Psoriasis and Depression group compared to controls ($P = 0.002$) while the Psoriasis group did not differ from the Psoriasis and Depression group ($P = 0.210$) or the control group ($P = 0.129$).

Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Psoriasis and Depression</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>46.11</td>
<td>11.10</td>
<td>47.96</td>
</tr>
<tr>
<td>Age of onset of psoriasis</td>
<td>.</td>
<td>.</td>
<td>32.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Psoriasis and Depression</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>8.0</td>
<td>28.6%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>20.0</td>
<td>71.4%</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>Yes</td>
<td>.0</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>.0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Comparing the two disease groups, regarding ESR, the initially observed differences at baseline remain statistically significant after adjusting for BMI, PASI score, BGA score, BSA score, DLQI score, BAI score, AIS score, age, gender, and treatment (P = 0.048). The differences, 3 months later, remain statistically significant (P = 0.025). Regarding CRP, the distribution of data is displayed by a boxplot-type of diagram in Figure 2.

Differences in ESR and CRP levels were examined between the two-time points (baseline and three months period) for the two groups of patients (Table 4). No significant changes in ESR or CRP values were observed in either group.

<p>| Table 2 Summarizes the clinical characteristics of individuals enrolled in the study |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Healthy controls</th>
<th>psoriasis+</th>
<th>depression</th>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriatic Nails</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>.0</td>
<td>0.0%</td>
<td>16.0</td>
<td>66.7%</td>
</tr>
<tr>
<td>No</td>
<td>.0</td>
<td>0.0%</td>
<td>8.0</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

TREATMENT FOR PSORIASIS:

| Treatment          | Conventional | N  | %  | N  | %  | N  | %  | N  | %  |
|--------------------|--------------|-----------------|-----------------|-----------------|
| Chemoprophylaxis   |              | .0 | 0.0% | 20.0 | 83.3% | 20.0 | 71.4% |
| Past               |              | .0 | 0.0% | 4.0  | 16.7% | 7.0  | 25.0% |
|                    |              | .0 | 0.0% | 0.0  | 0.0%  | 1.0  | 3.6%  |

MENTAL HEALTH:

<table>
<thead>
<tr>
<th>Family history of depression</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0</td>
<td>71.1%</td>
<td>3.0</td>
<td>12.5%</td>
<td>1.0</td>
<td>3.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.0</td>
<td>92.9%</td>
<td>21.0</td>
<td>87.5%</td>
<td>27.0</td>
<td>96.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Yes</td>
<td>.0</td>
<td>0.0%</td>
<td>3.0</td>
<td>12.5%</td>
<td>1.0</td>
<td>3.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>28.0</td>
<td>100.0%</td>
<td>21.0</td>
<td>87.5%</td>
<td>27.0</td>
<td>96.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CO-MORBIDITIES:

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.0</td>
<td>25.0%</td>
<td>9.0</td>
<td>37.5%</td>
<td>5.0</td>
<td>17.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.0</td>
<td>75.0%</td>
<td>15.0</td>
<td>62.5%</td>
<td>23.0</td>
<td>79.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Yes</td>
<td>.0</td>
<td>0.0%</td>
<td>5.0</td>
<td>20.8%</td>
<td>2.0</td>
<td>7.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>28.0</td>
<td>100.0%</td>
<td>19.0</td>
<td>79.2%</td>
<td>26.0</td>
<td>92.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>4.0</td>
<td>14.3%</td>
<td>3.0</td>
<td>12.5%</td>
<td>4.0</td>
<td>14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24.0</td>
<td>85.7%</td>
<td>21.0</td>
<td>87.5%</td>
<td>24.0</td>
<td>85.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Yes</td>
<td>4.0</td>
<td>14.3%</td>
<td>9.0</td>
<td>37.5%</td>
<td>8.0</td>
<td>28.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>24.0</td>
<td>85.7%</td>
<td>15.0</td>
<td>62.5%</td>
<td>20.0</td>
<td>71.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HEALTH HABITS:

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.0</td>
<td>53.6%</td>
<td>10.0</td>
<td>41.7%</td>
<td>16.0</td>
<td>57.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.0</td>
<td>46.4%</td>
<td>14.0</td>
<td>58.3%</td>
<td>12.0</td>
<td>42.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>Yes</td>
<td>10.0</td>
<td>35.7%</td>
<td>8.0</td>
<td>33.3%</td>
<td>19.0</td>
<td>67.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>18.0</td>
<td>64.3%</td>
<td>16.0</td>
<td>66.7%</td>
<td>9.0</td>
<td>32.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Use</td>
<td>Yes</td>
<td>.0</td>
<td>0.0%</td>
<td>.0</td>
<td>0.0%</td>
<td>1.0</td>
<td>3.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>28.0</td>
<td>100.0%</td>
<td>24.0</td>
<td>100.0%</td>
<td>27.0</td>
<td>96.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sports activity</td>
<td>Yes</td>
<td>8.0</td>
<td>28.6%</td>
<td>7.0</td>
<td>29.2%</td>
<td>4.0</td>
<td>14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>20.0</td>
<td>71.4%</td>
<td>17.0</td>
<td>70.8%</td>
<td>24.0</td>
<td>85.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SEX LIFE:

<table>
<thead>
<tr>
<th>Sexual activity</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
<th>Yes</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24.0</td>
<td>85.7%</td>
<td>15.0</td>
<td>62.5%</td>
<td>23.0</td>
<td>82.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>14.3%</td>
<td>9.0</td>
<td>37.5%</td>
<td>5.0</td>
<td>17.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual activity / affected by psoriasis</td>
<td>Yes</td>
<td>.0</td>
<td>0.0%</td>
<td>14.0</td>
<td>58.3%</td>
<td>7.0</td>
<td>25.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>.0</td>
<td>0.0%</td>
<td>10.0</td>
<td>41.7%</td>
<td>21.0</td>
<td>75.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The distribution of data is displayed by a boxplot-type of diagram in Figure 2.

Differences in ESR and CRP levels were examined between the two-time points (baseline and three months period) for the two groups of patients (Table 4). No significant changes in ESR or CRP values were observed in either group.
Figure 1. Comparative boxplot of erythrocyte sedimentation rate (ESR) baseline values.

Table 3. Distribution on erythrocyte sedimentation rate and C-reactive protein values in the three groups across the two time points

<table>
<thead>
<tr>
<th>Group</th>
<th>ESR at baseline</th>
<th>CRP at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>6.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Psoriasis and Depression</td>
<td>12.50a</td>
<td>50.00</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>5.00</td>
<td>28.00</td>
</tr>
</tbody>
</table>

* Significantly higher ESR levels versus patients with psoriasis
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

Table 4. Distribution on erythrocyte sedimentation rate and C-reactive protein values in the two groups across the two time points

<table>
<thead>
<tr>
<th>Group</th>
<th>ESR at baseline</th>
<th>CRP at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Psoriasis and Depression</td>
<td>12.50a</td>
<td>50.00</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>5.00</td>
<td>28.00</td>
</tr>
</tbody>
</table>

* Significantly higher erythrocyte sedimentation rate levels versus patients with psoriasis

no differences were observed between the two groups of patients at either time point.

Subgroup analysis indicated significantly higher ESR levels in women at 3 months (median=29, range=56), compared to men (median=4, range=39), P = 0.005. The Beck Anxiety score was positively correlated to CRP values at baseline (P = 0.027) and at 3 months as well (P = 0.009). Finally, higher CRP values were observed in patients with higher BMI value at baseline (P < 0.001).

Conclusions

The aim of the study was to investigate a potential significant difference in the levels of inflammatory markers CRP and ESR between patients with psoriasis and patients with psoriasis and depression. The potential influence of a three-month systematic treatment for psoriasis on the inflammatory
specific inflammatory marker as CRP, is influenced by other factors such as body weight [46], gender (female gender may be associated with increased prevalence of depressive symptoms [48] and levels of anxiety and insomnia [43]). We also know about the immunological background of depression and its relationship with the severity of psoriasis skin lesions [47,49] which affects different aspects of a patient life, including family and sexual life [50], and has an impact on the patient quality of life [50] and can lead, in more serious cases, to increased suicidal ideation [51].

The results of our study confirm the publications so far as we found significantly higher ESR in women with psoriasis and depression and higher CRP was observed in patients with higher BMI at baseline.

Regarding CRP and ESR, measurements were found higher CRP and ESR levels in patients with Psoriasis and Depression and Psoriasis vs healthy controls and higher CRP and ESR levels in patients with Psoriasis and Depression vs patients with Psoriasis. Instead, no significant changes in CRP or ESR values were observed between the two-time points (baseline and three months) after systemic therapy for psoriasis for the two groups of patients (Psoriasis and Depression and Psoriasis). We consider that the 3-month period between the 2 measurements was too short to allow safe conclusions on the possible reduction of CRP and ESR after systemic treatment for psoriasis that patients received.

Therefore, based our results of our study, it would be better to measure them at baseline. Their increased values can alert us not only to the possibility of co-morbidities such as psoriatic arthritis [52] or cardiovascular disease [53] or depression.

If it is also confirmed the existence of depression with the use of special questionnaires, such as Beck, it is an important help for us, as the treating doctors, of choosing the appropriate treatment for our patients suffering from psoriasis. In the literature, there are studies which found an improvement in the depressive symptoms of patients with psoriasis after systemic medication for psoriasis, and after the administration of specific biological factors [54,61] such as etanercept [55,56], adalimumab [57], ustekinumab [58,], while there are also drugs that can worsen it such as apremilast [59]. From Conventional drugs even though cyclosporine has been shown to inhibit Th1 and Th17 pathways exhibiting multifactorial and suppressive anti-psoriatic activity, its antidepressant activity has not been studied [60]. An older drug still used against psoriasis is methotrexate. The antidepressant effect of methotrexate has not been studied. Conversely, depressive symptomatology is reported as an adverse drug effect.

At the end it would be good to inform our patients about their condition and direct them to the appropriate specialist for them (psychiatrist or psychologist or both of them). Regarding pharmacologic treatment, there are studies that evaluated the efficacy of antidepressants, mainly selective serotonin reuptake inhibitors. Nowadays we know the role of the brain-skin axis [28] in psoriasis and depression, which among others leads to decreased serotonin levels. Serotonin is considered the “happiness hormone” because it affects mood and high levels of serotonin are associated with elevated mood and feelings of joy. Low levels of serotonin (serotonergic disbalance) are the key to pathophysiological mechanisms in depression [62]. Brain skin axis [28] by the release of the ACTH hormone, which has receptors among others in the skin, leads to the degranulation of mastocytes and the release of inflammatory factors: IFN-α and the IL-2, IL-6, IL1β, TNF-α by increasing the production of the enzyme Indoleamine 2,3-dioxygenase. This enzyme (Indoleamine 2,3-dioxygenase) catalyzes tryptophan into various other products. Serotonin is produced from tryptophan, resulting in decreased serotonin production due to reduced tryptophan and its products [63]. The relationship between the use of antidepressants for the treatment of depression and the reduction of inflammation and specifically the reduction of CRP has also been studied [64]. However, there is also an opinion that although antidepressants may alleviate psychiatric symptoms, there is evidence that they may be associated with psoriasis symptoms exacerbation [63]. Concerning other therapeutic approaches, a meta-analysis revealed encouraging results with respect to the psychotherapeutic interventions effectiveness on psoriasis outcomes [65]. Cognitive behavioral therapy may be a promising complementary approach for psoriasis patients with depressive symptoms [66]. Still, further research is warranted in this field. Positive psychology interventions strive towards consolidating psychological resources and nourishing positive cognitions and feelings [67].

In conclusion, psoriasis is a disease requiring a multidimensional therapeutic approach. Our study is based on limited and preliminary data. More studies are needed to help address this important correlation of specific inflammatory markers with the occurrence of depression in patients with psoriasis. The measurement of the values of CRP and ESR and their use to detect the possibility of the presence of depression can be an important tool for the holistic treatment of our patients with psoriasis.
References

2. Pr.C.E.M.Griffiths MD et al, Psoriasis, lancet, vol 397 april3, 2021
23. Dahl J, Ormstad H, Aass HC, et al. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. Psychoneuroendocri


Intralesional Quadrivalent Human Papilloma Virus Vaccine Versus Candida Antigen in the Treatment of Multiple Recalcitrant Non-Genital Warts

Ibrahim Fouda¹, Hassan Abou Khodair Mohammed¹, Ghada Mohammed Yousef Mohammed²

¹Dermatology, Venereology and Andrology Department, Damietta Faculty of Medicine, Al-Azhar University, Egypt
²Dermatology and Venereology Department, Talkha Central Hospital, Dakahlia, Egypt

Key words: warts, non-genital, recalcitrant, human papillomavirus vaccine, candida antigen

Introduction: Warts are the most prevalent clinical manifestation of Human Papilloma Virus (HPV) infections, which vary in morphological pattern depending on the site of the body affected.

Objectives: To evaluate the safety and efficacy of intralesional quadrivalent HPV vaccine versus candida antigen in treatment of multiple recalcitrant non-genital warts.

Methods: A randomized-control clinical trial included 60 cases with multiple recalcitrant warts who were randomly distributed into three groups; Group I included 20 patients who received intralesional candida antigen at a dose of 0.3 mL of 1/1000 solution, Group II included 20 patients who received intralesional quadrivalent HPV vaccine at a dose of 0.3ml and Group III included 20 patients who received intralesional injection 0.3 ml of normal saline 0.9% as a control group). Each agent was injected at the base of the largest wart every three weeks until it was completely cleared, or for a total of four sessions.

Results: The highest response rate was detected in the quadrivalent HPV vaccine group (75% complete response) followed by the candida vaccine group (40% complete response and 15% partial response). Also, regarding the distant response rate, the highest response rate was detected in the quadrivalent HPV vaccine group (72.7% complete response and 27.3% partial response) followed by the candida vaccine group (33.3% complete response and 50% partial response).

Conclusions: Intralesional immunotherapy appears to be effective and safe in treating multiple recalcitrant non-genital warts, with intralesional quadrivalent HPV vaccine outperforming intralesional candida antigen.
Introduction

Warts are benign epithelial proliferations resulting from more than 200 serotypes of Human Papilloma Virus (HPV) infection occurring on the skin and mucosa [1]. Warts are not life-threatening or harmful, but they can be embarrassing to the patient when present in the exposed areas of the body. Warts are infectious and can spread by skin-to-skin contact. However, the strains vary in their intensity of contagiousness [2].

Warts are categorized into two types: cutaneous and extracutaneous. Common warts, filiform warts, planter warts, plane warts, anogenital warts are among the cutaneous lesions. Oral common warts, oral condylomata acuminata, focal epithelial hyperplasia, oral florid papillomatosis, nasal papillomas, conjunctival papillomas, laryngeal papillomatosis, and cervical warts are extracutaneous lesions that affect the mucous membranes [3].

Unfortunately, a specific antiviral agent against HPV is lacking and while most warts spontaneously disappear, some persist and are resistant to treatment. All available treatment modalities intend to destroy lesions by chemical agents such as salicylic acid, 5-fluorouracil, and/or by physical destructive methods; eg (electrocautery, cryotherapy, photodynamic therapy and surgical excision). These methods, however might be associated with scarring, pain and high rates recurrence [4-6].

Intralesional antigen immunotherapy represents a promising therapeutic approach for the treatment of different types of warts, particularly if multiple and/or recalcitrant. Immunotherapeutic approaches act by enhancing the host cell-mediated immunity to eliminate the virus rather than just clearing the skin lesions [7].

The efficacy of immunotherapy using a single test antigen and multiple test antigens in the treatment of warts has been investigated with various degrees of success. Tuberculin purified protein derivative (PPD), measles, mumps, and rubella (MMR) vaccine, mycobacterium w vaccine, interferon-α or β, Candida antigen, and Bacillus Calmette-Guerin (BCG) vaccine are a few examples of immunotherapeutic drugs that have been researched [8-10]. The efficacy of Candida skin-test antigen in wart resolution was demonstrated in the first such trial [11].

Several studies have confirmed the role of a prophylactic quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) in the prevention of HPV-associated precancerous and cancerous lesions. There might be some cross-reactivity of antigenic epitopes in the HPV types covered by the vaccine and other HPV types responsible for common warts [12-14].

Objectives

In this study we aimed to evaluate and compare the safety and efficacy of intralesional Candida antigen versus quadrivalent HPV vaccine in treatment of multiple recalcitrant non-genital warts.

Methods

Patients

This is a three arm, single blinded, randomized controlled clinical trial included 60 cases.

Inclusion Criteria

patients who have multiple recalcitrant non-genital warts.

Recalcitrant warts were defined as warts that persisted for more than one year and were resistant to at least two therapeutic modalities.

Exclusion Criteria

patients on any treatment modality for warts during the last month prior to enrollment, pregnant and lactating females; patients with known hypersensitivity to Candida albicans antigen, with acute febrile illness, autoimmune disease or immunodeficiency were excluded from the study.

Assessments

All patients enrolled in the study were subjected to full history taking, general and dermatological examination to determine number, site, and size of warts and to detect presence or absence of distant warts or other skin diseases. Digital photography was done for all patients at baseline, follow up visits and after completion of treatment sessions.

Patients were randomly distributed into three equal groups:

Group I included 20 patients who received intralesional candida antigen at a dose of 0.3 mL of 1/1000 solution.

Group II included 20 patients who received intralesional quadrivalent HPV vaccine at a dose of 0.3 ml.

Group III included 20 patients who received intralesional injection 0.3 ml of normal saline 0.9% as a control group). Following the study completion, these patients were treated.

Each agent was injected every three weeks at the base of the largest wart until it was entirely removed or for a maximum of four sessions. The study was approved by an Ethics Committee of Damietta Faculty of Medicine IRB (00012367-20-12-004), Al-Azhar University, Egypt. Written informed consent was obtained from adult patients and parents of children included into the study.

Evaluation of the Clinical Response

The evaluation of therapeutic response was carried out by evaluating the size and counting the number of injected and distant warts by digital photographic comparison at baseline and at each visit. Complete response (disappearance of the warts and appearance of normal skin), partial response
Follow-up

A 6-month follow-up assessment was performed every month after the therapy was completed to detect any recurrence of warts.

Statistical Analysis

The data collected were coded, processed and analyzed with SPSS version 27 for Windows® (Statistical Package for Social Sciences) (IBM, SPSS Inc). Qualitative data as number (frequency) and percent was presented. The Chi-Square test (or Monte-Carlo test) made the comparison between groups.

The Kolmogorov-Smirnov test tested quantitative data for normality. Parametric data were expressed as median ± SD while the non-parametric data were expressed as median (Range). To compare three groups with normally distributed quantitative variables, one-way analysis of the variance (one-way ANOVA) test was used and Kruskal-Wallis test was used if the data were abnormally distributed. For all tests, P values <0.05 are considered significant.

Results

The study included 60 patients with multiple non-genital warts. The median age in group I was 16 years with range between 10 and 39 years, the median age in group II was 14 years with range between 9 and 34 years and the median age in group III was 20 years with range between 10 and 38 years. There was no statistically significant difference between the cases in the different studied groups regarding the age (P = 0.114).

As regards to the sex, there were 40% males and 60% females in group I, there were 35% males and 65% females in group II and there were 25% males and 75% females in group III with no statistically significant difference between the studied groups regarding the sex distribution (P = 0.293).

In regard to type of warts, in group I, the most common type of wart was common warts in 80% of the cases followed by plantar wart in 20% with no cases with plane warts in this group. In group II, the most common type of wart was common warts in 60% of the cases followed by plantar wart in 30% and plane warts in 10% of the cases. In group III, the most common type of wart was plantar warts in 85% of the cases followed by common wart in 15% with no cases with plane warts in this group.

As regards to number of warts, the median number of warts in group I was 3 with range between 3 and 13, the median number of warts in group II was 4 with range between 3 and 12 and the median number of warts in group III was 3 with range between 3 and 7. There was no statistically significant difference between the cases in the different studied groups regarding the number of warts (P = 0.282).

The median disease duration in group I was 20 months with range between 18 and 24 months, the median disease duration in group II was 24 months with range between 18 and 28 months and the median disease duration in group III was 20 months with range between 12 and 24 months. There was no statistically significant difference between the cases in the different studied groups regarding the disease duration (P = 0.059).

Presence of distant warts was reported in 30%, 55% and 15% in group I, II and III respectively with statistically significant difference between the studied groups (P = 0.025, Table 1).

Regarding the therapeutic response within the three studied groups, in group I, complete response was reported in 40% of the cases, partial response in 15% and no response in 45%. In group II, complete response was detected in 75% of the cases and no response in 25%. In group III, partial response in 10% of the cases and no response in 90% there was a statistically significant difference as regarding the local response between the three studied groups with the highest response in group II (quadrivalent HPV vaccine) followed by group I (Candida antigen).

Regarding the response in the distant warts within the three studied groups, in group I, complete response was detected in 2 out of 6 patients (33.3%), partial response in 3 out of 6 patients (50%) and no response in 1 out of 6 patients (16.7%). In group II, complete response was detected in 8 out of 11 patients (72.7%) and partial response in 3 out of 11 patients (27.3%). In group III, no distant partial or complete local response was detected. There was a statistically significant difference as regarding the response between the three studied groups with the highest response in group II (quadrivalent HPV vaccine) followed by group I (Candida antigen, Table 2).

Regarding the local side effects, tolerable pain during injection was reported in all the included cases. In group I, other local side effects included erythema in 30%, swelling in 30% and tenderness in 15% of the cases while in group II, erythema was detected in 25% of the cases.

Regarding the distant side effects, fever was detected in 55% and 10% in group I and group II respectively while bone ache was reported in 15% of the cases in group I only (Table 3).

No statistically significant difference in the adverse effects was observed between all studied groups.

No recurrence of warts was reported during the 6-month follow-up period in both groups.
Table 1. Baseline characteristics of the studied patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Candida antigen (N = 20)</th>
<th>Group II Quadrivalent HPV vaccine (N = 20)</th>
<th>Group III Normal saline (N = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>8 (40%)</td>
<td>7 (35%)</td>
<td>5 (25%)</td>
<td>0.293</td>
</tr>
<tr>
<td>Females</td>
<td>12 (60%)</td>
<td>13 (65%)</td>
<td>15 (75%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>16 (10-39)</td>
<td>14 (9-34)</td>
<td>20 (10-38)</td>
<td>0.114</td>
</tr>
<tr>
<td>Number of warts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>3 (3-13)</td>
<td>4 (3-12)</td>
<td>3 (3-7)</td>
<td>0.282</td>
</tr>
<tr>
<td>Duration of warts (Months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>20 (18-24)</td>
<td>24 (18-28)</td>
<td>20 (12-24)</td>
<td>0.059</td>
</tr>
<tr>
<td>Distant warts</td>
<td>6 (30%)</td>
<td>11 (55%)</td>
<td>3 (15%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Type of warts</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Common warts</td>
<td>16 (80%)</td>
<td>12 (60%)</td>
<td>3 (15%)</td>
<td></td>
</tr>
<tr>
<td>Plantar warts</td>
<td>4 (20%)</td>
<td>6 (30%)</td>
<td>17 (85%)</td>
<td></td>
</tr>
<tr>
<td>Planar wart</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td>0.468</td>
</tr>
<tr>
<td>Distant warts</td>
<td>6 (30%)</td>
<td>11 (55%)</td>
<td>3 (15%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>17 (85%)</td>
<td>18 (90%)</td>
<td>20 (100%)</td>
<td>0.236</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>19 (95%)</td>
<td>16 (80%)</td>
<td>18 (90%)</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Topical retinoid</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Electrotherapy</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>MMR intrallesional injection</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

HPV = Human Papilloma Virus.

Table 2. Therapeutic response among the studied patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Candida antigen (N = 20)</th>
<th>Group II Quadrivalent HPV vaccine (N = 20)</th>
<th>Group III Normal saline (N = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>8 (40%)</td>
<td>15 (75%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>9 (45%)</td>
<td>5 (25%)</td>
<td>18 (90%)</td>
<td></td>
</tr>
</tbody>
</table>

Distant response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Candida antigen (N = 6)</th>
<th>Group II Quadrivalent HPV vaccine (N = 11)</th>
<th>Group III Normal saline (N = 3)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2 (33 %)</td>
<td>8 (72.7 %)</td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (50 %)</td>
<td>3 (27.3 %)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>1 (16%)</td>
<td>0 (0%)</td>
<td>3 (100 %)</td>
<td></td>
</tr>
</tbody>
</table>

HPV = Human Papilloma Virus.
Table 3. Local and distant side effects among the studied patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Candida antigen (N = 20)</th>
<th>Group II Quadrivalent HPV vaccine (N = 20)</th>
<th>Group III Normal saline (N = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerable pain during injection</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Erythema</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>6 (30%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Tenderness</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Distant side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No distant lesions</td>
<td>9 (45%)</td>
<td>18 (90%)</td>
<td>20 (100%)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Fever</td>
<td>11 (55%)</td>
<td>2 (10%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Bone ache</td>
<td>3 (15%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

HPV = Human Papilloma Virus.

Conclusions

In general, practice, non-genital warts are a common. Despite following evidence-based treatment guidelines, a significant percentage of warts do not cure and become recalcitrant.

This current study was conducted to evaluate the efficacy of intralesional quadrivalent human papillomavirus (HPV) vaccine versus Candida antigen in treatment of multiple recalcitrant non-genital Warts.

The current study included 60 cases with multiple recalcitrant non-genital warts who were randomly distributed according to the treatment regimen into three groups; group I that included cases who received intralesional treatment with candida antigen, group II that included cases received intralesional treatment with quadrivalent HPV vaccine and group III that included cases received normal saline as a control group.

In the current study, the incidence of complete response after intralesional candida antigen was 40% and after intralesional injection of quadrivalent HPV vaccine was 75% with no cases with complete response in the control group. Also, partial response was noticed in 15% and 20% in the candida antigen group and control group respectively.

The rate of response to candida antigen was similar to many other studies including Signore (51%), Clifton et al (47%), Horn et al (54%), King et al (50%), Majid and Imran (56%), Alikhan et al (39%), and Nofal et al. (33.3%) [17-23].

An earlier study has shown higher response rate. Johnson et al showed 74% complete clearance of wart among studied group [24].

The disparities in the success rates between our study and the other related studies might be attributed to factors related to differences in the nature of the treated warts (multiple recalcitrant in our study), degree of HPV resistance and different HPV serotypes, and the number of the studied patients. Also, different injection regimens regarding the manufacturer of the antigen, the amount and concentration of the injected antigen per session, the number of the treatment sessions and the interval between the sessions.

Candida antigen works primarily by inducing Th1 cytokines including IFN- and IL-2, which stimulate cytotoxic and natural killer cells to eliminate HPV infection not only at the injection site but also at nearby and distant non-injected sites Nofal et al [25].

In the current study, regarding the distant response rate, the highest response rate was detected in the HPV vaccine group followed by the candida antigen group. In the candida antigen group, complete response was detected in 33.3%
and partial response in 50% while in the quadrivalent HPV vaccine group, complete response was detected in 72.7% and partial response in 27.3%.

This disagreed with Nassar et al who showed that the rate of resolution of distant, non-injected warts was 71.4% in the Candida group versus 41.2% in the HPV vaccine group [16].

The difference could be explained due to that the previous study used bivalent vaccine and our study used quadrivalent vaccine that provide greater cross-protection against HPV strains than provided by bivalent vaccine.

The mechanism of action of HPV vaccines in the treatment of warts is not yet established. This might be mediated by the development of IgG neutralizing antibodies directed against HPV-L1 capsid proteins generated as a result of vaccination. Although the HPV strains that cause common warts may be less genetically related to those implicated in cervical, vulvar, and anal cancer, it has been previously postulated that HPV vaccines can provide cross-protection against HPV strains other than those targeted by the individual vaccine administered [26,27].

The combination of drugs, with different mechanisms of action, has been postulated to improve treatment response, decrease adverse effects, and minimize recurrence rate. Many authors have reported better control of HPV infections using combined therapeutic modalities compared with monotherapy in the treatment of warts, particularly the recalcitrant ones [25,28].

One of the advantages of HPV vaccines is that the VLPs are not infectious, since they lack the virus DNA. Therefore, they can be used safely in case of immunosuppression, a major obstacle for other types of immunotherapies. Furthermore, the development of HPV-directed immunity after receiving the vaccine has a double benefit in the treatment of current infection and the prevention of future one [29].

In the current study, in the control group who received intralesional saline, local partial response was achieved in 10% of the cases with no distant response.

Fathy and his colleagues reported that intralesional injection of saline was associated with 20.7% good response and 79.3% poor response after the 5th session in cases with planter warts with no complete clearance of any wart [30].

Also, Mohamed and his colleagues reported a statistically significant decrease in the number of warts after 5 sessions of injection of intralesional saline of warts. The mechanism of action of intralesional saline is unknown; it may be due to exposure of the viral particles to the immune system that later attacks them through the trauma produced during the injection [31].

The difference between our study and these studies may be explained by the differences in the nature of the treated warts (recalcitrant in our study) as the duration of the warts show a significant inverse correlation with the treatment response (the longer the duration, the lower the response). Also the number of the treatment sessions (5 sessions versus 3 sessions in our study).

The main strength point of the current study, the first to evaluate the effectiveness of the quadrivalent HPV vaccine in comparison to the candida antigen and the placebo.

However, the current study had some limitations as it is a single center study and recruited a relatively small sample size that could decrease the power of the obtained results, and there was no efficacy analysis taking into account the size and duration of the lesions. Also, the short duration of follow up did not enable to comment on the long-term outcomes especially the rate of recurrence.

Based on our findings, intralesional antigen immunotherapy seems to be an effective therapeutic option for the treatment of non-genital warts. Additionally, we came to the conclusion that the efficacy of intralesional quadrivalent HPV vaccine was superior to intralesional candida antigen.

---

**Figure 1.** Male patient 21-year-old with multiple common warts on both hands (A) before, (B) after treatment with intralesional candida antigen.
Figure 2. Female patient 15-year-old with multiple common warts on the right hand (A) before, (B) after treatment with intralesional quadrivalent HPV vaccine.

References


Serum Levels of IL-35, One of the Newest Members of Interleukin-12 Family of Cytokines, in Patients With Vitiligo

Yıldız Hayran¹, Çiğdem Yücel², Esra Fırat Öğuz³, Funda Eren³, Turan Turhan³, Başak Yalçın⁴

Department of Dermatology, Ankara City Hospital, Ankara, Turkey
2 Department of Medical Biochemistry, University of Health Sciences, Gülhane Teaching and Research Hospital, Ankara, Turkey
3 Department of Medical Biochemistry, Ankara City Hospital, Ankara, Turkey
4 Dermatology, Private Practice, Ankara, Turkey

Key words: vitiligo, cytokine, interleukin-12 family, disease characteristics

Citation: Hayran Y, Yücel Ç, Fırat Öğuz E, Eren F, Turhan T, Yalçın B. Serum Levels of IL-35, One of the Newest Members of Interleukin-12 Family of Cytokines, in Patients With Vitiligo. Dermatol Pract Concept. 2024;14(2):e2024069.
DOI: https://doi.org/10.5826/dpc.1402a69

Accepted: October 11, 2023; Published: April 2024

Copyright: ©2024 Hayran et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: This study was supported by a research grant from the Turkish Society of Dermatology (2019/78).

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Yıldız Hayran, Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya, 06800, Ankara, Turkey. Tel: +90312 552 60 00 Fax: +903123126876 E-mail: yildiz_kantarci@yahoo.com

ABSTRACT

Introduction: Vitiligo is a chronic skin disorder in which immune dysregulation has been reported as one of the major etiopathological factors. Interleukin-12 (IL-12), IL-23 and IL-27 of IL-12 cytokine family were identified as critical cytokines in the pathogenesis of many autoimmune and inflammatory skin diseases including vitiligo. IL-35 is one of the newest member of IL-12 cytokine family.

Objectives: The purpose of our study was to examine serum IL-35 levels in addition to serum IL-12, IL-23, IL-27 levels in the vitiligo patients and control group, and to investigate the relationship of these cytokines with the characteristics of vitiligo.

Methods: Serum IL-12, IL-23, IL-27 and IL-35 levels of 87 vitiligo patients and 70 healthy volunteers were analyzed using the enzyme-linked immunosorbent assay (ELISA). We compared the IL-12 cytokine family levels in the patient and control groups, and investigated the relationship of these levels with the characteristics of vitiligo.

Results: Patients had higher levels of IL-12 (31.2 versus 20.1, P < 0.001) and IL-35 (9.6 versus 8.1, P = 0.031). Patient and control groups had similar levels of IL-23 (P = 0.78) but were correlated with the Vitiligo Area Scoring Index (VASI) (P = 0.022, r = 0.35). Patients had lower levels of IL-27 (207.6 versus 258.7, P < 0.001). In addition, the levels of serum IL-27 were correlated negatively with the Vitiligo Disease Activity (VIDA), and positively with disease duration (P = 0.007, r = 0.30).

Conclusions: Differences of serum levels between Vitiligo patients and healthy controls, significant relationships with the characteristics of vitiligo suggest that the IL-12 cytokine family may play a role in the pathogenesis of vitiligo.
Introduction

Vitiligo is an autoimmune disorder characterized by depigmented patches on the skin, skin appendages and mucous membranes. Its frequency is approximately 1%. Although vitiligo most commonly develops before the second decade, it can occur in any age group [1]. Even if it is not mortal, it may cause many psychological problems including anxiety, depression and sleep disorders that seriously affects the quality of life [1,2].

The pathogenesis of vitiligo has not been fully defined but oxidative stress and immune dysregulation are thought to be the fundamental causes of vitiligo in genetically predisposed individuals [3]. Oxidative stress and similar other internal and external stimuli cause the release of inflammatory cytokines, which in turn stimulates the innate immune response, and a series of reactions that result in the activation of adaptive immune response and autoreactive CD8+ T cells [3]. The role of interleukins in the pathogenesis of vitiligo is also well known. Many interleukins including primarily IL-17, and IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-19, IL-23 and IL-33 have been examined in vitiligo patients. Significant relations have been shown between the dysregulation of interleukin levels and clinical factors such as the degree and extensiveness of the disease [4].

The IL-12 family consists of IL-12, IL-23, IL-27, and IL-35 [5,6]. These cytokines are heterodimeric and consist of an alpha subunit (p19, p35, or p28) and a beta subunit (p40 or Epstein-Barr virus induced gene 3, EBI3) [5]. Cytokines of the IL-12 family bind to heterodimeric receptors and act through the JAK-STAT signaling pathway [5]. Although, the members of this cytokine family have common subunits in its structure and receptors, they have different functions. IL-12, IL-23, IL-27 and IL-35 may have pro-inflammatory or anti-inflammatory effects by affecting different T lymphocyte subsets. IL-12 and IL-23 are mostly pro-inflammatory, IL-35 is mostly anti-inflammatory, while IL-27 shows pro-inflammatory and anti-inflammatory properties at different times [5,6].

Although the IL-12 cytokine family has been studied in many inflammatory and neoplastic diseases, few studies investigated its effects on vitiligo, and major differences were found between the results of those studies [7].

Objectives

The purpose of the present study was to investigate the levels of serum IL-12, IL-23, IL-27 and IL-33 in patients with vitiligo compared to healthy controls, and identify the relations between cytokine levels and clinical features.

Methods

Eighty-seven (52 females, 35 males) vitiligo patients and 70 healthy controls were included in the study. Patient and control groups were similar in terms of age and sex (P = 0.51 and 0.39, respectively).

The patients were clinically diagnosed with vitiligo. Patients who came to the dermatology outpatient clinic with complaints of skin discoloration were evaluated. Patients with hypopigmented/depigmented macules and patches were examined under WOOD light, and patients with depigmented patches matching the definition of vitiligo were included in the study. Patients with lesions spreading segmentally were excluded from the study even if they were diagnosed with vitiligo.

Vitiligo Activity and Severity Index (VASI) was used to determine the extent of vitiligo, and vitiligo disease activity score (VIDA) was used to evaluate the disease activity of vitiligo. The Vitiligo Disease Activity Score (VIDA) is a six-point scale that is used to evaluate the vitiligo disease activity. The VIDA score is evaluated as +4 = active for the last 6 weeks, +3 = active for the last 3 months, +2 = active for the last 6 months, +1 = active for the last 1 year, 0 = stable over the last year, -1 = stable with spontaneous re-pigmentation over the last year” [8]. The age of onset, duration of the disease, presence of additional autoimmune disease, presence of vitiligo in the family, and presence of additional autoimmune disease in the family were recorded based on a detailed history taken from the patients. All participants gave written informed consent prior to the study.

Examination of IL-12 Cytokine Family Level

Venous blood samples were collected from all participants after 12 hours of fasting. Blood samples collected for analysis were centrifuged at 4000 rpm for 10 minutes. Separated sera were aliquoted into Eppendorf tubes and stored at -80 °C until the time of analysis. Serum IL-12, IL-23, IL-27 and IL-35 levels were detected with human ELISA (double antibody sandwich ELISA method) kits according to manufacturer instructions (manufacturer: USCN Life Sciences). All values are expressed as pg/mL. Intra-Assay CV values were less than 10% and inter-assay CV values were less than 12% for all parameters.

Statistical Methods

The data were analyzed using SPSS/IBM for windows 21.0. Descriptive statistics such as percentage, mean, median, standard deviation and interquartile range (IQR) were used to define the sample. The assumption of conformity to the normal distribution was examined using the Shapiro Wilk test. The difference between the means of two independent groups was analyzed by the Student t test in cases where parametric test assumptions were met, and the difference
between the medians of two independent groups was analyzed by Mann-Whitney U test in cases where parametric test assumptions were not met. Spearman or Pearson tests were used to evaluate the correlation between two numerical values. Categorical data were analyzed with the Chi-square significance test or Fisher Exact test. A 95% level of significance (error margin: \( \alpha = 0.05 \)) was used to determine the statistically significant differences in the analyses.

### Results

#### Demographic and Clinical Features of Study Population

Fifty-nine point eight percent of the vitiligo patients were female and 40.2% were male. The mean age of the patients was 39.8 years (SD=13.2 years). 55.2% (N = 48) of the patients had generalized vitiligo and 34.5% (N = 30) had localized vitiligo. The median VASI was 4 (IQR = 1.18-10.3). The age of onset was 26 (IQR = 13-40) and the duration of the disease was 8 months (IQR = 2-21 months). The VIDA score was “-1” for 23%, “0” for 12.6%, “1” for 10.3%, “2” for 19.5%, “3” for 8.4%, and “4” for 3.4% of the patients. While 29.9% of the patients had a history of non-vitiligo autoimmune disease, 21.8% had a family history of vitiligo, and 21.8% had a family history of non-vitiligo autoimmune disease.

#### Serum IL-12, IL-23, IL-27, and IL-35 Concentrations in Vitiligo Patients and Control Group

Serum IL-12, IL-23, IL-27, and IL-35 concentrations in vitiligo patients and control group are summarized in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Vitiligo</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-12 (pg/mL), median (IQR)</td>
<td>31.2 (25.4-42.1)</td>
<td>20.1 (13.3-32.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-23 (pg/mL), median (IQR)</td>
<td>25.1 (19.9-31.8)</td>
<td>21.8 (18.9-72.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>IL-27 (pg/mL), mean (SD)</td>
<td>207.6 (71.3)</td>
<td>258.7 (85.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-35 (pg/mL), median (IQR)</td>
<td>9.6 (5.8-20.8)</td>
<td>8.1 (5.1-11.3)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

IQR = interquartile range; SD = standard deviation.

![Figure 1](image1.png)

**Figure 1.** Comparison of serum IL-12, IL-23, IL-27, and IL-35 concentrations in vitiligo and control groups (***P < 0.001, *P < 0.05).
and 258.7 (SD=85.5) in controls. Serum IL-27 levels were statistically lower in patient group compared to healthy controls (P < 0.001) (Figure 1). Serum IL-23 levels were similar among patient and control groups (P = 0.78) (Figure 1).

**Association of the IL-12 Cytokine Family With Patient Demographics and Vitiligo Disease Characteristics**

Serum IL-12, IL-23, IL-27, and IL-35 levels were similar among male and female patients (P = 0.93, 0.25, 0.79, and 0.96, respectively). Serum IL-23 levels positively correlated with age (P = 0.025, r = 0.34) but no statistically significant correlation was observed between age and serum IL-12 (P = 0.19, r = -0.11), IL-27 (P = 0.29, r = 0.12), and IL-35 (P = 0.91, r = -0.01) levels.

Serum IL-12, IL-23, IL-27, and IL-35 levels were similar among vitiligo patients with localized and generalized vitiligo (P = 0.44, 0.16, 0.49, 0.32, respectively). While there was a significant correlation between the VASI value and IL-23 (P = 0.022, r= 0.35), VASI and Serum IL-12 (P = 0.74, r=-0.04), IL-27 (P=0.11, r=0.18), and IL-35 (P=0.49, r=-0.08) levels were not correlated (Figure 2). VIDA scores and IL-27 levels were negatively correlated. Patients with high VIDA scores and active disease had significantly lower levels of IL-27 (P = 0.024, r = -0.26). No correlation was observed between VIDA and serum IL-12 (P = 0.79, r = -0.03), IL-23 (P = 0.58, r = -0.08) or IL-35 (P = 0.91, r = -0.01) levels.

Vitiligo age of onset and the levels of IL-12, IL-23, IL-27, or IL-35 were not found to be correlated (all P values > 0.05), but IL-27 levels and disease duration were positively correlated (P = 0.007, r = 0.30). The correlation between the disease duration and IL-23, IL-27 or IL-35 level is shown in the Figure 3.

Patients with and without a non-vitiligo autoimmune disease, patients with and without a family history of vitiligo, and patients with and without a family history of non-vitiligo autoimmune disease had similar levels of serum IL-12, IL-23, IL-27, and IL-35 (all P values > 0.05).

![Figure 2](image_url). The correlation between Vitiligo Area Scoring Index (VASI) and the interleukin-12 family of cytokines.
the release IFN-γ and the development of T helper type 1 (Th1) immune response, eliminating intracellular bacteria and viruses and stimulating inflammation [9,10].

In our study, we found significantly higher levels of serum IL-12 in Vitiligo patients compared to healthy volunteers. In a study on innate pro-inflammatory cytokines in patients with vitiligo, Gholijani et al found high levels of serum IL-12, which was consistent with our findings [11]. IL-12 may play a role in the pathogenesis of vitiligo by affecting many pathways. IL-12 is known to activate type 1 cytotoxic CD8 T cells to direct the granzyme and perforin-mediated cytotoxic activity [10]. IL-12 may also contribute to the formation of vitiligo by affecting the presentation of autoantigens. In a study on generalized vitiligo patients, Singh et al investigated the relationship between IL-12 levels and dendritic cell counts of the vitiligo and control groups. They found an increase in dendritic cells in addition to an increase in serum IL-12 levels in the vitiligo group. The authors stated that increased dendritic cell frequencies and proinflammatory cytokines including IL-12 may be associated with defective antigen presentation [7].

Conclusions

We compared the levels of IL-12, IL-23, IL-27 and IL-35 in vitiligo patients and healthy volunteers. Patients had higher levels of IL-12 and IL-35, and lower levels of IL-27. While patient and control groups had similar IL-23 levels, serum IL-23 levels were correlated with the extensiveness of the disease. We observed a negative correlation between serum IL-27 levels and VIDA scores, and a positive correlation between disease duration and serum IL-27 levels.

IL-12 is released from dendritic cells, macrophages and B cells in response to internal and external stimuli. Comprised of p40 and p35 subunits, IL-12 exerts its effect by binding to the heterodimeric receptor that is made up of the IL-12Rβ1 and IL-12Rβ2 subunits. Binding of IL-12 to the receptor activates Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2), phosphorylating STAT4 for biological effects [9]. IL-12 is a proinflammatory cytokine and it performs these functions mainly through its effects on T cell differentiation and functions. Recognition of pathogens by an antigen-presenting cell stimulates the production of IL-12, which in turn stimulates the release IFN-γ and the development of T helper type 1 (Th1) immune response, eliminating intracellular bacteria and viruses and stimulating inflammation [9,10].

In our study, we found significantly higher levels of serum IL-12 in Vitiligo patients compared to healthy volunteers. In a study on innate pro-inflammatory cytokines in patients with vitiligo, Gholijani et al found high levels of serum IL-12, which was consistent with our findings [11]. IL-12 may play a role in the pathogenesis of vitiligo by affecting many pathways. IL-12 is known to activate type 1 cytotoxic CD8 T cells to direct the granzyme and perforin-mediated cytotoxic activity [10]. IL-12 may also contribute to the formation of vitiligo by affecting the presentation of autoantigens. In a study on generalized vitiligo patients, Singh et al investigated the relationship between IL-12 levels and dendritic cell counts of the vitiligo and control groups. They found an increase in dendritic cells in addition to an increase in serum IL-12 levels in the vitiligo group. The authors stated that increased dendritic cell frequencies and proinflammatory cytokines including IL-12 may be associated with defective antigen presentation [7].

Figure 3. The correlation between vitiligo duration and the interleukin-12 family of cytokines.
Additionally, IL-12 helps the differentiation of naive CD4+ T cells into interferon (IFN)-γ producing Type 1 T helper (Th1) cells and stimulates IFN-γ production from natural killer (NK) cells [5]. The role of IFN-γ in the pathogenesis of vitiligo is known well. IFN-γ increases the expression of CD8+ T lymphocyte accumulations were observed around the hair follicles in lesions with vitiligo. Even though IL-12 is known to trigger a Th1 response, observation of vitiligo in mice with depleted CD4+ T cells raised the question of whether IL-12 alone is enough for the development of vitiligo and whether additional pathways are needed for the development of vitiligo [12].

In our study, patient and control groups had similar serum IL-23 levels but there was a significant correlation between IL-23 levels and disease severity. Only a limited number of studies examine serum IL-23 levels and their relations with disease characteristics. In two different studies conducted by Vaccaro et al. and Nieradko-Iwanicka et al, vitiligo patients had higher serum IL-23 levels than the control group [13, 14]. On the other hand, Osman et al. found in a study comparing 42 adult vitiligo patients and 43 healthy controls that the patient and control groups did not have any significant difference in terms of IL-23 levels, which was consistent with our study [15]. Studies also differ greatly in terms of the relationship between serum IL-23 levels and disease characteristics. While Vaccaro et al. reported a positive correlation between serum IL-23 levels and disease duration, extent of vitiligo and severity of the disease, Osman et al. did not find a correlation between IL-23 and disease duration [13,15]. Nieradko-Iwanicka et al. investigated the association between IL-23 and diseases severity and reported that patients with an involved body surface area <10% and >10% were similar in terms of serum IL-23 levels [14].

IL-23 (comprised of p40 and p19 subunits) exerts its effect by binding to the heterodimeric receptors that are made up of the IL-12Rβ1 and IL-23R subunits. Once IL-23 binds to the receptor, JAK2 and TYK2 are activated. Activated JAK2 and TYK2 than phosphorylate STAT3 and STAT4 accomplishing its biological effects [9]. The biological activity of IL-23 is generally proinflammatory. IL-23 stimulates IL-17 and/or IL-22 production from Th17 cells, group 3 innate lymphoid cells (ILC3), γδ T cells and IL-17-producing CD8+ T (Tc17) cells, and plays a role in stabilization of Th17 cells [9, 10]. Although the main role of IL-23 in the pathogenesis of vitiligo has not been fully understood, there are abundant data supporting the effect of IL-17 in the development of vitiligo [16,17]. Vitiligo patients have higher levels of IL-17 and more Th17 cells in peripheral blood than controls. Vitiligo tissues have Th17 cell infiltration and increased IL-17 mRNA expression. In addition, in-vitro studies showing that IL-17 reduces melanin production and causes shrinking in melanocytes supports the possible role of IL-17 in the pathogenesis of vitiligo [16,17]. Stimulating Th17 cell differentiation, hence production of IL-17 cytokines, IL-23 may contribute to the pathogenesis of vitiligo directly or through Th17/IL-17 pathway.

Although IL-12 and IL-23 are thought to play a role in the pathogenesis of vitiligo, whether IL-12/IL-23 blockers can be used in the treatment of vitiligo is not clear. IL-12/23 inhibitors have very different effects on vitiligo lesions. Patients administered IL-12/23 inhibitors have reported formation of de novo vitiligo, which either improves inflammation and repigmentation of depigmented patches [18,19].

Serum IL-27 levels were lower in vitiligo patients compared to controls. IL-27 levels of vitiligo patients had been analyzed in a previous study. Hosseini et al. compared IL-27 levels of 79 vitiligo patients and 45 healthy controls, and reported lower IL-27 levels in vitiligo patients in parallel with our results. The study did not report any correlation between IL-27 levels and gender, extensiveness of the disease in terms of body surface area, type of vitiligo, and treatment responses [20]. We could not find any correlation between IL-27 levels and extensiveness of the disease either, but IL-27 levels were negatively correlated with the disease activity. Patients with active vitiligo had lower levels of IL-27, patients with a stable course of disease had higher IL-27 levels. IL-27 levels were also correlated with disease duration. The fact that IL-27 was lower in patients with a shorter disease duration and a higher activity score suggests that IL-27 may play a role in formation of vitiligo patches at early stages of the pathogenesis of vitiligo.

IL-27 was thought to be a pro-inflammatory cytokine since it stimulates the production of interferon-γ (IFN-γ) from T cells, and natural killer cells (NK), increases adhesion molecules on the T cell surface, and improves the function of CD8+ T cells [21]. However, a growing number of studies have supported the anti-inflammatory properties of IL-27 in recent years. IL-27 shows a suppressive effect by stimulating the production of IL-10, supporting the growth and survival of Treg cells, stimulating the expression of inhibitory
receptors on the T cell surface, and suppressing dendritic cells [21]. Vitiligo patients having lower levels of IL-27 than controls suggests that IL-27 may play an immunosuppressive role in vitiligo.

Although serum levels of IL-12, IL-23 and IL-27 have been studied in vitiligo, the effect of IL-35 in vitiligo is yet to be identified. Serum IL-35 levels were also higher in vitiligo patients compared to controls in our study. IL-35 is mainly produced by regulatory T cells (Treg), active macrophages and B cells. Comprised of EB3 and p35 subunits, IL-35 operates by binding to its heterodimeric receptor (GP130–GP130, IL-12Rb2–IL-12Rb2, IL-12Rb2–GP130, and GP130–IL-12Rb1). IL-35 binding to the receptor activates JAK1 and JAK2. STAT1, STAT3, and STAT4 are than phosphorylated for biological effect [22]. Different receptors on the surfaces of cells may have different biological effects by activating different JAKSTAT pathways. IL-35 receptors on Treg cells and Breg cells enable IL-35 to stimulate expansion in Treg and Breg cells, creating immunosuppressive effects [23].

IL-35 serum levels have been previously studied in many autoimmune and inflammatory diseases and different outcomes reported. Compared to healthy controls lower serum IL-35 levels were reported in patients with systemic lupus erythematosus and rheumatoid arthritis, whereas higher levels of IL-35 were seen in patients with systemic sclerosis [23,24].

Even though the reason for the increased levels of IL-35, which has an anti-inflammatory and immunosuppressive cytokine, in autoimmune/inflammatory diseases is not fully known, several studies have attempted to explain this contradiction. In a study investigating whether IL-35 has different properties from IL-10, transforming growth factor (TGF)-β or similar other anti-inflammatory cytokines, Li et al. showed that IL-35 was a stimulable anti-inflammatory cytokine unlike other anti-inflammatory cytokines [25]. IL-35 prevents inflammation from reaching its maximum impact rather than preventing inflammation from forming by being expressed in response to inflammatory stimuli [25]. Qiu et al. found higher levels of serum IL-35 in patients with active Lupus compared to controls, and observed a reduction in IL-35 levels after treatment. The authors argued that IL-35 was an anti-inflammatory factor that increased to antagonize the negative impact of the pathological inflammation to a certain extent [26]. Correlation of IL-35 with sedimentation levels in patients with primary Sjögren syndrome backs the arguments that IL-35 is an anti-inflammatory cytokine that is secreted secondarily to inflammatory stimuli to antagonize the effects of maximal inflammation [24].

Although vitiligo patients had higher levels of IL-35 than healthy controls, there was not any significant correlation between serum IL-35 levels and the extensiveness or activity of the disease. In vitiligo IL-35 may be expressed to antagonize the maximal effects of pro-inflammatory cytokines as is the case with lupus and primary Sjögren disease.

Levels of IL-12, IL-27 and IL-35 from the IL-12 cytokine family were not similar for vitiligo patients and healthy volunteers. Vitiligo patients had higher levels of IL-12 and IL-35, and lower levels of IL-27. Also, lower levels of IL-27 were clearer in patients with a higher disease activity and a shorter duration of vitiligo. IL-23, which had similar serum levels in the patient and control groups, was correlated with VASI. This study showed that in addition to previously studied IL-12 cytokines (IL-12, IL-23, IL-27), IL-35, one of the newest members of IL-12 family, may also play a role in the pathogenesis of vitiligo.

References


Dermoscopic Features of Pigmented Bowen Disease: A Multicenter Study on Behalf of the Ibero-Latin American College of Dermatology (CILAD)

Horacio Cabo1, Gabriel Salerni2, Emilia Cohen Sabban3, Agustín Bollea Garlatti4, Nicole Orendain5, Sonia Rodríguez-Saa6, Renato Marchiori Bakos7, Flavia Carolina Pozzobon8, Virginia M González9, Rosario Peralta10, Cristian Navarrete-Dechent11, 12, Dominga Peirano12, Elia Pérez-Fernández13, Susana Puig14

1 Head Professor of Dermatology, Universidad de Buenos Aires, Argentina
2 Dermatology Department, Hospital Provincial del Centenario de Rosario - Universidad Nacional de Rosario, Rosario, Argentina
3 Head of Dermatology Service, Instituto de Investigaciones Médicas Alfredo Lanari, Universidad de Buenos Aires, Argentina
4 Private practice, San Miguel de Tucumán, Tucumán, Argentina
5 Private practice, Guadalajara, Mexico
6 Department of Dermatology, Hospital Nuestra Señora del Carmen, Obra Social de Empleados Públicos (OSEP), Godoy Cruz, Mendoza, Argentina
7 Department of Dermatology, Hospital de Clínicas de Porto Alegre - Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
8 Centro de Diagnostico Dermatológico, Bogotá, Colombia; Instituto Nacional de Cancerología, Bogotá, Colombia
9 Dermatology Department, Hospital Alemán, Buenos Aires, Argentina
10 Dermatology Department, Instituto de Investigaciones Médicas “A. Lanari”, University of Buenos Aires, Buenos Aires, Argentina
11 Melanoma and Skin Cancer Unit, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
12 Department of Dermatology Pontificia Universidad Católica de Chile, Santiago, Chile
13 Unidad de Investigación. Hospital Universitario Fundación Alcorcón, Madrid, Spain
14 Melanoma Unit, Hospital Clinic Barcelona, University of Barcelona, Barcelona, Spain. CIBER de enfermedades raras, Instituto de Salud Carlos III, Barcelona, Spain

Key words: Bowen disease, dermoscopy, pigmented Bowen disease, skin cancer, diagnosis


Accepted: October 2, 2023; Published: April 2024

Copyright: ©2024 Cabo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Gabriel Salerni, Salta 2391. CP 2000. Rosario. Argentina. Phone: +54 341 4398586
Email: gabrielsalerni@hotmail.com
Introduction

Bowen disease (BD) is a form of squamous cell carcinoma in situ that shows full-thickness involvement of the epidermis, and the pilosebaceous units. In the case of pigmented Bowen disease (pBD), the distinguishing feature is the presence of pigmentation or dark coloration within the lesion [1].

Clinically, pBD appears as a well-defined, dark brown or black patch on the skin, often resembling melanoma or other pigmented skin lesions. It typically occurs on sun-exposed areas of the body, such as the face, scalp, neck, and hands, although it can appear elsewhere as well. The lesion may be flat or slightly raised, and it can be associated with symptoms like itching or tenderness [1].

Dermoscopy has shown to be a valuable tool in the diagnosis of skin cancer, by providing enhanced visualization, improving diagnostic accuracy, and enabling early detection of both melanoma and non-melanoma skin cancer [2-6]. The dermoscopic features of pBD have been already described in Caucasian European population [7]; however, studies focused on Latin American population are scarce and limited to case reports or small series.

Herein, we report dermoscopic findings in a large series of pBD in Latin American patients, with most patients being skin phototype 3 and 4. Distinctively in our study, the pigmented structures and the clues derived from the presence of melanin were much more frequent than in previous reports in fair skin.

Objectives

To report dermoscopic findings in a large series of 147 pBD diagnosed in Ibero-Latin American population.

Methods

We conducted a retrospective analysis of clinical and dermoscopic characteristics of 147 histologically proven pBD retrieved from the database of 22 institutions (private and academic centers), planned as a project of the Dermoscopy Chapter of the Ibero-Latin American College of Dermatology (CILAD). All active CILAD members were invited to participate in the study, the call was made through periodic mails/reminders through the CILAD mailing list for a period of 3 months. We included cases of biopsy-proven pBD with clinical and dermoscopic pictures. We excluded patients were either clinical or dermoscopic photos were missing or if the images were of poor quality.

Clinical data such as age, gender, previous history of skin cancer and skin phototype of the patients and the evolution, localization and diameter of the lesions were recorded. The clinical and dermoscopic images were evaluated by 2 experts dermoscopists (G.S. and H.C.) who performed both clinical and dermoscopic evaluation. Dermoscopic images were assessed for the presence or absence of criteria for pBD as previously described [7-10]. If the two observers did not agree on any point of the clinical and dermoscopic evaluation, a consensus ruling was applied to reach agreement.

Statistical Analysis

The data was analyzed with the SPSS 22 program. The distribution of the qualitative data is presented by means of absolute and relative frequencies and the distribution of the
quantitative data by mean and standard deviation or median and interquartile range, depending on the distribution of the data. The estimates of the dermoscopic findings are presented, accompanied by the corresponding 95% confidence intervals calculated by the exact method.

Results

Population
A total of 147 pBD analyzed. The study population consisted of 77 females (52%) and 70 males (48%) with mean age of 68.6 (range 40-94) years. Regarding skin phototype, 103 (70.1%) corresponded to skin phototype 3, 23 (15.6%) phototype 2, and 21 (14.3%) phototype 4. A total of 40 patients had previous history of basal cell carcinoma (27.2%), 26 of squamous cell carcinoma (17.7%), and 9 (6.1%) of melanoma.

Clinical Evaluation
Median size of the lesions was 13 mm (interquartile range [IQR] 10-19). Fifty lesions (34%) were located on lower extremities, 28 (19%) in upper extremities, 23 (15.6%) on head and neck, 22 (15%) on anterior trunk, 14 (9.5%) on posterior trunk, and 10 (6.8%) on other localizations. The median time to diagnosis was 18 months (IQR 12-24) and it was unknown in 34 cases (23.1%).

On clinical examination, near 60% of pBD were flat (N = 87), 70% (N = 104) presented with scales, and 90% (N = 133) were asymmetric.

Dermoscopic Evaluation
Dermoscopy evaluation is shown in Table 1. Regarding dermoscopic features, structureless areas were observed in most cases (92.5%, N = 136), followed by dots in more than 70% of cases (N = 105); circles were observed only in 8.2% of the cases (N = 12). Brown and pink colors were the most frequent, observed in 98 and 94.6% respectively; white color was observed in 52.7% and gray color in 36.7%. Blue and black colors were observed both in only 3.4% of cases.

The most prevalent dermoscopic clues to pBD observed were: structureless hypopigmented areas in 91.8% (N = 135), vessels arranged in linear fashion at the periphery in 62.6% (N = 92), and pigmented lines or pigmented dots in linear arrangement in 59.2% (N = 87). Clustered, coiled, and dotted vessels were observed in 55.8% (N = 83), 45.6% (N = 77), and 45.6% (N = 67), respectively. Only 9.5% (N = 14) displayed no specific dermoscopic clues upon examination (Figure 1).

<table>
<thead>
<tr>
<th>Table 1. Dermoscopic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N = 147</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Features</strong></td>
</tr>
<tr>
<td>Structureless</td>
</tr>
<tr>
<td>Dots</td>
</tr>
<tr>
<td>Circles</td>
</tr>
<tr>
<td><strong>Color</strong></td>
</tr>
<tr>
<td>Brown</td>
</tr>
<tr>
<td>Pink</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Gray</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Blue</td>
</tr>
<tr>
<td><strong>Dermoscopic clues</strong></td>
</tr>
<tr>
<td>Hypopigmented structureless areas</td>
</tr>
<tr>
<td>(white, pink, or skin colored)</td>
</tr>
<tr>
<td>Vessels distributed in a linear</td>
</tr>
<tr>
<td>fashion</td>
</tr>
<tr>
<td>Vessels distributed in a linear</td>
</tr>
<tr>
<td>fashion at the periphery</td>
</tr>
<tr>
<td>Pigmented lines or dots distributed</td>
</tr>
<tr>
<td>in a linear fashion</td>
</tr>
<tr>
<td>Clustered vessels</td>
</tr>
<tr>
<td>Coiled vessels</td>
</tr>
<tr>
<td>Dotted vessels</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Figure 1. Examples of pBD, clinic (top row) and dermoscopic images (bottom row). Dermoscopic clues observed are as follows: (A) Dotted vessels arranged in a linear fashion at the periphery, (B) Clustered glomerular vessels, (C) Hypopigmented structureless areas and dotted vessels, and (D) Hypopigmented structureless areas, glomerular and dotted vessels.

Conclusions

It has been almost 30 years since the first descriptions of the dermoscopic features of pBD, evidence suggest that dermoscopy has been shown to be useful in improving its diagnostic accuracy. Early in 2004, Zalaudek et al reported the presence of glomerular vessels in combination with a scaly surface as the most frequent criteria in both pigmented and non-pigmented BD; the authors additionally reported the presence of small brown globules and/or homogeneous pigmentation in the pigmented variety [7].

Also in 2004, Bugatti et al reported that pigmented structures could be detected by dermoscopy in many cases of their series including 14 cases, such as the presence of pseudo-network, irregular diffuse pigmentation, and irregular dots / globules [8]. Shortly after, Stante et al reported a lesion of pBD clinically mimicking a superficial spreading melanoma; they describe a reticular, heterogeneous arrangement of the melanin pigment, which might resemble therefore remnants of atypical pigment network, and irregular, brown globular structures at the periphery and wide regression-like areas [9].

In 2010, Cameron et al. described the dermoscopic patterns of pBD in a series of 52 cases. They characterized two archetypical dermoscopic patterns of pBD, namely a structureless brown pattern and a combination of dots and structureless pattern. They also identified a linear arrangement of brown and/or gray dots and/or coiled vessels that have not been described previously in other lesions and represented a specific clue to pBD [10].

Few data exist about the characteristics of the population corresponding to the first cases describing dermoscopic findings in pBD. In 2009, Mun et al described the dermoscopic features of 26 BD in Asians, of which 10 were pigmented, they reported the presence of small brown globules, small black globules, and structureless (homogenous) pigmentation as the most frequent findings [11]. In 2010, Gutierrez-Mendoza et al reported two cases of pBD in skin phototypes 3 and 4. Both cases displayed irregular dotted vessels and pigment remnants upon dermoscopy [12].

Our study provides novel and useful information on the dermoscopic characteristics of pBD in a specific population. Since it is a study on behalf of CILAD, it is the first study that includes mostly Latin American patients:142 out of 147 corresponded to patients from Argentina, Brazil, Chile, Colombia, and Mexico. The remaining 5 cases corresponded to patients from Spain. In line with this, we found 70% of patients with skin phototype 3 and almost 15% with skin phototype 4. Similar to the findings from Cameron et al [10], the most frequently observed feature in our study were structureless areas in more than 90% of the cases and dots in 70%. Regarding color, brown and pink were the most frequent observed in more than 90% of the cases.

Regarding dermoscopic features, hypopigmented (pink, skin colored, or white) structureless areas were the most
frequent structure followed by vascular structures and pigmented lines or dots arranged in linear fashion. In our series, dermoscopic clues concerning melanin structures were more frequent than in the series from Cameron et al [10]. Although the latter study did not describe skin types, as this was a study from Australia and Austria, it could be assumed that the majority were patients with fair skin phototypes, and this could explain the lesser frequency of pigmented structures.

Our study does not lack of limitations since it was a retrospective study and evaluators were not blinded to the diagnoses.

We report a large series of cases of pBD in Latin American patients, with most patients having skin phototype 3 and 4. In this population, the pigmented structures and the clues derived from the presence of melanin are much more frequent than in previous reports in fair skin patients.

Acknowledgments: We would like to thank the collaboration of the following colleagues for providing cases for the study: Blanca Carlos, Consuelo Mosquera, Dianely García-Hernández, Diana Guerrero Hernández, Sofia André, Cinthia López Kot, Rocio Muñiz, Ivonne Arellano, Malynahi Tapia Juárez, Luis Carlos Morales Godínez, Luisa Polo Silveira, Mayra Reyes Soto

References


Real-World Experience of Tofacitinib and Baricitinib Use in Alopecia Areata in Greek Population: A Retrospective Analysis With Focus on Safety

Zoe Apalla1, Efterpi Zafiriou2, Effimia Zagkliverinou3, Angeliki-Viktoria Roussaki-Schulze2, Polyxeni Gidarokosta2, Niki Ntavari2, Stella Sakellaropoulou1, Maria Boziou1, Anastasia Emvalomati1, Eirini Kyrmanidou1, Elizabeth Lazaridou1

* E. Kyrmanidou and E. Lazaridou equally contributed in their role as Senior authors.

1 Second Dermatology Department, Aristotle University of Thessaloniki, Thessaloniki, Greece
2 Department of Dermatology, University General Hospital Larissa, University of Thessaly, Larissa, Greece
3 Internal Medicine Department, “Theagenio” Hospital, Thessaloniki, Greece

Key words: alopecia areata, janus kinase inhibitors, tofacitinib, baricitinib, real-world

DOI: https://doi.org/10.5826/dpc.1402a73
Accepted: October 2, 2023; Published: April 2024

Copyright: ©2024 Apalla et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Zoe Apalla, PhD, address: K. Karamanli 60, 54643, E-mail address: zoimd@yahoo.gr, Tel. +306972916729

ABSTRACT

Introduction: The introduction of Janus Kinase inhibitors (JAKi) seems to revolutionize the field of alopecia areata (AA) therapeutics. However, real-world data are still missing.

Objectives: To provide evidence about effectiveness and safety of tofacitinib and baricitinib in AA in real-world settings and describe baseline disease characteristics and patients profiles that are considered good candidates for JAKi in the daily practice. Furthermore, we intended to investigate potential correlations between baseline characteristics and treatment outcomes.

Methods: We retrospectively reviewed the databases of two tertiary Hospitals in Greece, to identify individuals of any age currently being treated with systemic JAKi for severe AA.

Results: We identified 42 individuals, including 3 adolescents. In our cohort, 52.3% (22/42) were under tofacitinib and 47.6% (20/42) under baricitinib treatment. Efficacy analysis was performed on the subgroup of 30 patients that had completed at least a 3-month follow-up on treatment. In the latter group, mean time on treatment was 10 months. Mean Severity of Alopecia Tool and mean Dermatology Life Quality Index scores decreased from 84.46% and 12.86 at baseline, to 43.26% and 6.63, respectively. Complete response (CR) was recorded in 4 (13.33%), partial in 12 (40%) and no response in 14 patients (46.66%), correspondingly. Seventeen out of 42 (40.5%) individuals in total, reported at least 1 adverse event. No patient required hospitalization. Among 15 patients (35.7%) who got COVID-19, one suffered from serious infection. The 3 adolescents achieved CR with no significant adverse events.

Conclusions: Real-world data suggest efficacy and safety of JAKi in severe forms of AA. Tolerability is optimal in younger individuals.
Introduction

Alopecia areata (AA) is a non-scarring alopecia that greatly affects patients’ quality of life. Disease severity depends on the extent of the body area involvement, ranging from mild severity in localized forms (plaque type AA) to severe generalized clinical types of AA, such as alopecia totalis (AT) or alopecia universalis (AU). Topical and intralesional steroids are considered first-line therapeutic modalities for localized plaque type AA, while systemic use of steroids and other immunomodulating agents are preserved for generalized forms of the disease. Despite their beneficial effect on AA, conventional treatments have been linked to important side-effects and high rates of recurrence after treatment cessation that limit their use.

After many years of scant or no development in the area of AA therapeutics, the introduction of Janus Kinase inhibitors (JAKi) seems to revolutionize the field, providing promising treatment outcomes in severe forms of the disease [1]. The mode of action of JAKi implicates intracellular interruption of the JAK-STAT pathway. Tofacitinib is a potent, selective inhibitor of the JAK family (JAK 1/3), approved for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis in adults and juvenile idiopathic arthritis in patients ≥ 2 years of age. Tofacitinib, though not officially indicated, was the first drug of the group of JAKi used in AA. Recently, FDA approved baricitinib for the treatment of severe AA. Baricitinib exerts its effects by inhibiting JAK1 and JAK2 enzymes.

Data emerging from real-world settings in regards with the use of JAKi in AA are limited [2-5].

Objectives

In the current study, we aimed to provide evidence about effectiveness and safety of the use of tofacitinib and baricitinib for AA in real-world settings and describe baseline disease characteristics and patients profiles that are considered good candidates for JAKi in the daily practice. Furthermore, we intended to investigate potential correlations between baseline characteristics and treatment outcomes.

Methods

Towards the aims of the study, we retrospectively reviewed the databases of two tertiary Hospitals in Greece for the last five years, to identify individuals of any age currently being treated with systemic JAKi for severe AA. The standard of care for AA in both centers conforms to the published guidelines and depends on the clinical type, disease severity, age of the patient and response to previous treatments. The study received Institutional Ethical Committee approval.

Upon their first visit, all patients provide written informed consent for collecting their data, and history and physical and dermatoscopic examination is carried out. Disease severity is determined by the use of the Severity of Alopecia Tool (SALT) that estimates the extent of alopecia in percentages. ΔSALT score was used as a variable in order to assess the percentage change observed in SALT score at baseline and at the most recent follow-up visit for each patient. Treatment response was classified as no response (NR) with <30% of regrowth, partial response (PR) with 30%-90% of regrowth and complete response (CR) with >90% of regrowth. Patients were also asked to fill in a Dermatology Life Quality Index (DLQI) questionnaire in Greek. Clinical and dermatoscopic photos were collected and saved in the databases. Efficacy outcomes were obtained from individuals that had completed at least a 3-month follow-up period on treatment, whilst safety outcomes emerged from the whole studied group. According to the regulations in Greece, before prescribing JAKi to our patients for any indication, we have to ask for approval by the National Medical Organization. Spearman correlation and Kruskal-Wallis tests were used to compare the variables using IBM SPSS Statistics version 29.0. Statistical analyses were performed using IBM SPSS Statistics version 29.0.

Results

Demographics and Baseline Clinical Characteristics

We identified 42 individuals (25 females and 17 males), including 3 adolescents. The mean age was 39.5 (SD: 14.4, range: 13-60 years). All participants suffered from severe AA (mean baseline SALT score 80.21% [SD 24.09%]). Patients sociodemographic and clinical characteristics are summarized in Table 1.

The mean time since AA first onset and last AA episode were 8.28 and 3.32 years, correspondingly. Mean baseline SALT score was 80.21% (SD: 24.09%) and the mean baseline DLQI score was 12.59 (SD: 3.96). Statistically significant difference was recorded in mean baseline DLQI score between men (11.15) and women (14.17, P = 0.04), whilst no statistically significant difference was observed in the corresponding mean SALT scores (mean baseline SALT for men was 78.38% and 89.11% for women, P = 0.161). The latter observation indicates that AA has a greater impact on females as compared to males.

The most frequent clinical type of alopecia areata in this cohort was universalis (40.4%), followed by plaque type AA covering 25-75% of the scalp (16.6%) and totalis seen in 14.2%. Family history of AA was reported by 26.1% (11/42) of the patients, while 52.3% (22/42) could not recall other first- or second-degree relatives suffering from AA. From the
Table 1. Epidemiologic and clinical characteristics of the patients included in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographic features</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>39.52 (14.48)</td>
</tr>
<tr>
<td>Time since first onset, years mean (SD)</td>
<td>8.28 (10.73)</td>
</tr>
<tr>
<td>Sex Male, % (N)</td>
<td>40.47% (17/42)</td>
</tr>
<tr>
<td>Sex Female, % (N)</td>
<td>59.52% (25/42)</td>
</tr>
<tr>
<td>Time since last episode of AA, years, mean (SD)</td>
<td>3.32 (4.16)</td>
</tr>
<tr>
<td><strong>Previous treatments, % (N)</strong></td>
<td></td>
</tr>
<tr>
<td>topical steroids</td>
<td>76% (32/42)</td>
</tr>
<tr>
<td>intralesional injections</td>
<td>45.2% (19/42)</td>
</tr>
<tr>
<td>topical calcineurin inhibitors</td>
<td>14.2% (6/42)</td>
</tr>
<tr>
<td>DPCP</td>
<td>14.2% (6/42)</td>
</tr>
<tr>
<td>Anthralin</td>
<td>9.5% (4/42)</td>
</tr>
<tr>
<td>systemic cortisone</td>
<td>71% (30/42)</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>52% (22/42)</td>
</tr>
<tr>
<td>JAKi</td>
<td>4.7% (2/42)</td>
</tr>
<tr>
<td>PRP</td>
<td>9.5% (4/42)</td>
</tr>
<tr>
<td>hydroxychloroquine</td>
<td>4.7% (2/42)</td>
</tr>
<tr>
<td><strong>Comorbidities, % (N)</strong></td>
<td></td>
</tr>
<tr>
<td>thyroid disease</td>
<td>38% (16/42)</td>
</tr>
<tr>
<td>myasthenia gravis</td>
<td>4.7% (2/42)</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>4.7% (2/42)</td>
</tr>
<tr>
<td>vitiligo</td>
<td>2% (1/42)</td>
</tr>
<tr>
<td>hypertension</td>
<td>4.7% (2/42)</td>
</tr>
<tr>
<td>asthma</td>
<td>2% (1/42)</td>
</tr>
<tr>
<td>rheumatoid arthritis</td>
<td>2% (1/42)</td>
</tr>
<tr>
<td><strong>Severity of the disease</strong></td>
<td></td>
</tr>
<tr>
<td>Basal SALT score mean (SD)</td>
<td>80.21 (24.09)</td>
</tr>
<tr>
<td>Current SALT score mean (SD)</td>
<td>43.27 (39.44)</td>
</tr>
<tr>
<td><strong>Treatment characteristics</strong></td>
<td>Baricitinib</td>
</tr>
<tr>
<td>Mean treatment time (months)</td>
<td>2.7</td>
</tr>
<tr>
<td>Maintenance dose (mg/day)</td>
<td>4mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jaki=Janus kinase inhibitor; PRP=Platelet Rich Plasma; SALT = Severity of Alopecia Tool; SD=Standard deviation;

recorded comorbidities, thyroid disease was the first in the list, found in 38% (16/42) of the participants.

The most common previously used treatments were topical steroids (32/42), systemic steroids (30/42), cyclosporine (22/42), and intralesional steroids (19/42). Adverse events to previous treatment included hypertension (~41%), hypertrichosis (~35%), Cushing syndrome (~35%) and topical atrophy (~17%).

In our cohort, 52.3% (22/42) of the patients were under tofacitinib and 47.6% (20/42) under baricitinib and the mean time on current treatment was 7.4 months (SD: 6.46, range: 1-30 months).

Table 1 summarizes patients epidemiological and clinical characteristics.

Clinical Outcomes

Mean time on treatment of all participants was 7.4 months (SD 6.46, 1-30), whilst mean time to first signs of hair regrowth was 2.66 months. All patients on baricitinib received the recommended dose of 4 mg per day. In this group one patient switched from tofacitinib due to treatment failure (started with 10mg/day for 6 months and 20 mg/day for 3 months with no response and continued afterwards with
Figure 1. Efficacy analysis of 30 individuals that had completed at least 3 months on treatment with Janus Kinase inhibitors revealed a significant reduction in mean Severity of Alopecia Tool (SALT) and Dermatology Life Quality Index (DLQI) scores from baseline to the last follow up visit (mean treatment time 10 months).

4 mg/day baricitinib). The maintenance dose for all the 20 patients receiving baricitinib was 4 mg/day.

In the tofacitinib group, 21 patients started with 10 mg/day, except from one patient who started with a daily dose of 5mg, due to history of metabolic syndrome. This individual had developed Cushing syndrome due to the previous long-term use of systemic steroids. After 11 months of tofacitinib, he switched to baricitinib, due to lack of efficacy. Five patients from the tofacitinib group received a maintenance dose of 20 mg/day, whilst 17 of them received a maintenance dose of 10 mg/day. For all patients under tofacitinib the maximum dose was 20 mg/day for 1-6 months, depending on treatment tolerance. The maintenance dose was determined by the response to treatment and the patient’s tolerance to the drug.

All the 3 adolescents that were treated with tofacitinib, experienced >90% of hair regrowth.

Efficacy Analysis and Correlations

Efficacy analysis was performed on the subgroup of 30 patients that had completed at least a 3-month follow-up on treatment. The rest twelve patients that had not completed the first 3-month follow-up visit were excluded, due to lack of efficacy data at this time point.

In the 30 individuals analyzed, the mean time on treatment was 10 months. Their mean SALT and mean DLQI scores decreased from 84.46% and 12.86 at baseline, to 43.26% and 6.63, respectively. CR was recorded in 4 patients (13.33%), PR in 12 patients (40%) and no response in 14 patients (46.66%) patients. Figure 1 illustrates clinical examples of the three groups. There was statistically significant difference in the treatment duration among the 3 response subgroups (p= 0.002). The majority of non-responders (64.2%) belonged to the group of AU.

No statistically significant differences were observed between sex and ΔSALT score and thus effectiveness does not appear to be related to sex (P = 0.323, two-sided test). We divided the patients into three age groups (< 25 years, 25-50 years and > 50 years) and we found no statistical correlation between ΔSALT score and age (p=0.693). ΔSALT score did not significantly differ among the 7 clinical types of alopecia areata (P = 0.207, the significance level is 0.05) and was not affected by time since the last episode of AA (r; 0.373, P > 0.05). All performed correlations are presented in Table 2.

Table 2. Correlations and non-parametric tests

<table>
<thead>
<tr>
<th>Correlations</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSALT score and patient age</td>
<td>r; 0.596, p&gt;0.05</td>
</tr>
<tr>
<td>ΔSALT score and patient age (among the 3 age groups)</td>
<td>P = 0.693</td>
</tr>
<tr>
<td>ΔSALT score and clinical types of AA</td>
<td>P = 0.207</td>
</tr>
<tr>
<td>ΔSALT score and time since last episode of AA</td>
<td>r; 0.373, p&gt;0.05</td>
</tr>
<tr>
<td>Clinical response and treatment duration</td>
<td>P = 0.002</td>
</tr>
</tbody>
</table>

AA = AA: alopecia areata; SALT = Severity of Alopecia Tool.
**Table 3. The most common adverse events in patients with alopecia areata treated with baricitinib and tofacitinib in our cohort**

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated liver enzymes and lipid elevation</td>
<td>4.7</td>
</tr>
<tr>
<td>Lipid elevation</td>
<td>9.5</td>
</tr>
<tr>
<td>COVID-19 infection</td>
<td>35.7</td>
</tr>
<tr>
<td>• mild symptoms</td>
<td>19.0</td>
</tr>
<tr>
<td>• moderate symptoms</td>
<td>9.5</td>
</tr>
<tr>
<td>• serious symptoms</td>
<td>2.3</td>
</tr>
<tr>
<td>• asymptomatic</td>
<td>4.7</td>
</tr>
<tr>
<td>Herpes zoster and herpes simplex</td>
<td>2.3</td>
</tr>
<tr>
<td>None</td>
<td>59.5</td>
</tr>
</tbody>
</table>

**Safety Outcomes**

Twenty five out of 42 (59.5%) individuals experienced no adverse events (AE), whilst 17/42 (40.5%) reported at least 1 AE, during JAKi treatment. Thirteen patients (30.9%) presented with one AE, 7.1% (3/42) presented with two and 2.3% (1/42) presented with three AE. No patient required hospitalization for JAKi-related AE. Fifteen patients (35.7%) got COVID-19 infection during treatment. Among them, two out of 42 (4.7%) individuals were totally asymptomatic, 8/42 (19%) presented with mild infection (fever up to 37.5°C, myalgia, weakness and cough) and 4/42 (9.5%) presented with moderate symptom (fever up to 38.5°C for 2 days, weakness and sore throat). One individual (2.3%) suffered from serious COVID-19 disease (fever up to 40°C for 3 days, headache, cough, weakness). It is of particular importance to report that the 3 adolescent patients did not experience any kind of AE or laboratory abnormalities, except of persistent common warts in one of them. Table 3 summarizes the AEs observed in our cohort.

**Conclusions**

Severe AA is a challenging-to-treat immune mediated disorder, characterized by treatment resistance and high recurrence rate. Until recently, there were no safe and effective treatments for AA that could offer consistent and long-lasting results. Topical, intraleisonal and systemic treatment with corticosteroids, contact immunotherapy, and systemic immunomodulating drugs as cyclosporine, methotrexate and azathioprine have been administered with variable efficacy outcomes, although the abovementioned agents are used as off label treatments in cases of AA [6].

In the last years, several studies on tofacitinib, baricitinib and other JAK inhibitors have demonstrated encouraging outcomes [7]. Tofacitinib and baricitinib showed to be effective and well-tolerated also in our cases of AA, achieving almost 50% reduction in the mean SALT score. Furthermore, 16/30 patients responded to treatment, and 13.33% achieved an improvement in the SALT score of >90%. Similar results were recorded by Kenedy Crispin et al in an open-label study, evaluating the use of oral tofacitinib and reporting 64% of patients responding to the therapy and 32% of them achieving a SALT score reduction >50%. Accordingly, Liu et al report >50% improvement in SALT score in 42% of their patients [8]. Similar, were the results from the BRAVE-AA1 and BRAVE-AA2 clinical trials where 19.7% and 34% of patients achieving SALT≤20 in the 2 and 4 mg baricitinib arms, respectively [9,10]. A recent meta-analysis of JAKi in the treatment of AA, reported that from 289 patients, there were 45.7% good responders, and 21.4% partial responders. Interestingly, the researchers found no difference in the response rates between tofacitinib, baricitinib, and ruxolitinib [11]. Our treatment response rates comply with that from other trials and we confirm the efficacy of these new drugs in treating AA at a real world setting. Except of tofacitinib and baricitinib, efficacy of upatacitinib in AA has been evaluated in a study including patients concomitantly suffering from both, atopic dermatitis and AA. The investigators recorded a significant reduction of the mean SALT score from baseline (95.1 ±9.6) to the 4th week of treatment (77.6 ± 28.2, P = 0.0087), highlighting that the group of JAKi opens a new horizon in the treatment of AA [12].

In our studied population we included 3 adolescents and no statistical correlation was identified regarding the efficacy outcome and the age of the patient. In this specific age group, no differences were identified regarding the adverse events recordings. Similarly low is the adverse event rate from analogous studies [13-15].

Our observations also pose a few questions regarding treatment handling during infections [16,17]. From the meta-analysis report, the most common adverse events observed are upper respiratory (18.2%), urinary tract infections (2.2%) and total infections (24.6%) [11]. The observation period of our study included the COVID-19 pandemic period and maybe this is the reason for the high incidence of COVID-19 infection rates recorded. Whether treatment with JAKi should be discontinued, as advised in cases of other chronic inflammatory diseases, is under discussion.

Considering COVID-19 disease, our results indicate that JAKi have a satisfactory safety profile, as long as patients are compliant and discontinue treatment during infection [18]. Although there are reports proposing JAKi as a potential treatment for COVID-19, we recommend JAKi discontinuation, especially in symptomatic patients.

Overall, complication rates and adverse events during treatment with JAKi are low, and so far, no hospitalization
for JAK inhibitor-related adverse events is reported in the literature.

Addressing safety and efficacy of SARS-CoV-2 vaccination in patients receiving immunotherapeutics, Gresham et al outlines that there is a possibility of decreased immune response and vaccine immunogenicity in patients on systemic immunotherapies, particularly in patients receiving azathioprine, cyclosporine, methotrexate, or JAKIs [19]. Additionally, Seror et al conducted a study in order to investigate the immune response to COVID-19 vaccination in patients treated with JAKIs. 113 patients with rheumatoid arthritis or psoriatic arthritis receiving baricitinib (56/113, 50%), tofacitinib (30/113, 27%) or upadacitinib (27/113, 24%) were included and their immune response to COVID-19 vaccination was evaluated. The overall response rate to the vaccine in patients treated with JAKIs remained high. Non-responders were mostly older patients, and patients receiving upadacitinib. Serological assessment 2 weeks after vaccination should be recommended for patients aged 65 years and older or treated with upadacitinib to secure a high safety profile [20].

In conclusion, our results demonstrate that tofacitinib and baricitinib are effective and safe therapeutic modalities for AA in real-world settings. Currently, only baricitinib is officially indicated for AA.

Limitation of our study is the short follow up on treatment and the small number of participants.

References


Triamcinolone Injection in the Treatment of Malar Edema

Wioleetta Barańska-Rybāk1, Zuzanna Święczewska1, Agnieszka Lemiec2, Lee Walker3

1 Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdańsk, Poland
2 La Estetica Clinic, Płock, Poland
3 B City Clinic, Liverpool, England

Key words: malar edema, aesthetic medicine, filler injection, hyaluronic acid


Accepted: December 7, 2023; Published: April 2024

Copyright: ©2024 Barańska-Rybąk et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Wioleetta Barańska-Rybąk, Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdańsk, Poland. E-mail: wioletta.baran ska-rybak@gumed.edu.pl

ABSTRACT

Introduction: Tear-through deformities can be a detectable sign of facial aging. Over recent years, minimally invasive procedures such as hyaluronic acid filler injections have been shown to be effective in improving this area. Malar edema is the accumulation of fluid over the malar eminence persisting for 1 month or more. Given its nature, the management remains problematic. The most commonly reported treatment modality is injection with hyaluronidase.

Objectives: To determine the safety and efficacy of triamcinolone injection in the treatment of malar edema.

Methods: A total of 15 female patients with malar edema, with a mean age of 43.77 years, were treated with triamcinolone injections. The volume injected was chosen by the investigator. Prior to the triamcinolone injection, all patients had been treated with hyaluronidase, which turned out to be ineffective in all cases. Patients were asked to note all adverse effects.

Results: Satisfactory results were achieved after a single treatment session for 14 patients and after two treatments for one patient. Overall, injections with triamcinolone were well tolerated and no adverse reactions were reported.

Conclusions: Injection with triamcinolone appears to be a safe and effective option for the management of malar edema following hyaluronic acid filler injection. Nevertheless, further research with larger patient groups is compulsory.
Introduction

Tear-through deformities can be a detectable sign of facial aging; hence, rejuvenation of this area is essential to restore a more refreshed and youthful appearance. Over recent years, minimally invasive procedures such as hyaluronic acid (HA) filler injections have been shown to be effective in improving this area. Yet with the tear trough being recognized as the most challenging area to treat with HA filler and the spectrum of complications, such as swelling, bruising, Tyndall effect, or malar edema, it may pose a challenge especially when performed without proper precaution.

Malar edema is the accumulation of fluid over the malar eminence persisting for 1 month or more. It has been reported with an incidence between 11%-25% of tear trough filler treatments [1,2]. The underlying cause of malar edema after dermal filler injection is most likely due to a band of connective tissue, called a malar septum, which divides the superficial suborbicularis oculi fat into a superficial and deep compartment. Although the lymphatic drainage of the deep compartment is contiguous with the cheek drainage, the superficial compartment lymphatic drainage is compromised [3]. This complication is proposed to be multifaced and related to the depth of injection, the volume injected, the patient degree of preprocedural lymphatic obstruction, and the physical qualities of the injectate [4]. Given its nature, the management of malar edema remains problematic. The most commonly reported treatment modality is injection with hyaluronidase nonetheless, in clinical practice it has not proven to be effective in all cases thus new therapeutic options are emerging [5,6].

Triamcinolone is a corticosteroid widely used in dermatology for a variety of conditions, including keloids, hypertrophic scars, alopecia areata, granuloma annulare, or acne [7-10]. Regardless of its common use, the availability of reliable guidelines is still lacking.

Objectives

The aim of this study is to report 15 cases with malar edema post tear-trough augmentation successfully treated with triamcinolone injection and to determine the safety and efficacy of triamcinolone injection in the treatment of malar edema.

Methods

A total of 15 female Caucasian patients, with a mean age of 43.77 years (range, 35-56 years), presented to our clinics in Poland complaining of malar edema. All 15 patients presented with bilateral edema following tear-trough augmentation with hyaluronic acid, with no signs of erythema, soft and not tender to the touch. Duration of the last filler injection varied from 1 month to 1.5 years before experiencing the edema. The injections were performed by dermatologists or beauticians in different clinics. Patients injected by a beautician were unaware of the amounts, nor the brand of the injected filler. Various brands of fillers were applied among patients injected by dermatologists. Demographic and clinical data, including comorbidities and previous procedures, have been collected. No patient had any history of previous lower eyelid blepharoplasty, allergies, chronic malar edema of unknown origin, infection, or thyroid disease. None of the patients were injected with permanent fillers before. Prior to treatment, patients were subjected to a brief general examination including an ultrasound examination performed by a trained practitioner. Each examination revealed subcutaneous tissue edema with no filler residue, and no granulomas.

Each patient was treated by triamcinolone injection per side directly into edema with cannula retrograde under ultrasound. The volume injected was chosen by the investigator (10 mg/1mL, 0.5 mL per each side with a TSK 25G 38 mm cannula). Patients were asked to note all adverse effects. Prior to the triamcinolone injection, all patients had been treated with hyaluronidase, which turned out to be ineffective in all cases. Different kinds and volumes of hyaluronidase were used by the injectors who performed tear trough treatment with HA and the authors have no knowledge regarding the used products nor amounts.

Photographs were obtained at the baseline before every treatment session, after one week from the triamcinolone injection for evaluation of treatment response, and after additional 3 months for follow-up. Moreover, the evaluation of the subject general health was performed during each visit.

Results

The treatment response was evaluated by 2 independent practitioners after 1 week of the triamcinolone injection. Satisfactory results in the form of edema reduction were achieved after a single treatment session for fourteen patients and after two treatments for one patient. Overall, injections with triamcinolone were well tolerated and no signs of edema could be detected after the product administration. No cases of skin atrophy, hypopigmentation, or necrosis were observed. Any other adverse reactions were also not reported. At the 3-month follow-up, all patients remained asymptomatic and full resolution of edema was maintained. All 15 patients reported high satisfaction with the treatment applied which was evaluated using a questionnaire prepared for the purpose of this study (Figure 1).
Conclusions

Fillers with hyaluronic acid have become one of the most popular nonsurgical facial treatments for the infraorbital area. There is a growing awareness of the vascular risks associated with HA-based filler injections that can result in blindness. Nonetheless, the use of such fillers in the infraorbital region should generally be considered as safe. The data regarding late complications (2–4 weeks or longer post-injection) of HA fillers is rather sparse, which could be a result of both low incidence and the fact that most complications can be treated relatively easy, the second of which may result in a lack of reporting. Malar edema tends to occur days to weeks after injection however, it has also been reported to arise several years post-injection [11]. Although malar edema can be somewhat mitigated, such complication cannot be fully eluded.

The underlying cause of malar edema is yet to be fully elucidated, since various theories have been proposed. Due to the rather impenetrable malar septum which divides the superficial sub-orbicularis oculi fat into a superficial and deep compartment, the tear trough region is specifically prone to edema. When injected too superficial to the malar septum, dermal fillers may hinder lymphatic drainage and result in malar edema. On the other hand, deeper injections, especially with a high water affinity filler or with too great of a volume, may give rise to direct compression of the lymphatic vessels. What is more, the hypothesis has been given that at particular risk for developing edema are patients burdened with allergies, rosacea, or preexisting malar edema however, it has not been confirmed [11]. In order to reduce the incidence of malar edema, adequate filler, and patient selection, limiting filler volume, and placing the product deep into the malar septum are generally advised [12,13].

Since its first introduction in 1961, intralesional injection with corticosteroids has been an important part of dermatological treatment [14]. Intralesional injections are found to be useful for a variety of indications, are simple to administer, and are relatively safe. The aim behind intralesional therapy is to inject medicine directly into a particular skin region in order to treat local tissues while having minimal systemic effects. One of the most widely injected corticosteroids is triamcinolone. Due to its known, anti-angiogenic, anti-inflammatory, anti-proliferative, and

Figure 1. The results of the treatment with triamcinolone injections.
especially anti-edematous effects, triamcinolone has great potential in the treatment of malar edema [15-17]. Although the administration of triamcinolone has multiple benefits, it is not without ramifications. Among the most common side effects atrophy, telangiectasia, and hypopigmentation can be distinguished, thus it is of high importance to be aware of the occurrence of such events [18]. It is of high importance to use a proper dilution and a minimal amount to achieve satisfactory results.

A study by Siperstein et al discussed the use of triamcinolone in the infraorbital region in aesthetic medicine when 1 mg of triamcinolone was mixed with a 1-cc syringe of hyaluronic acid filler for the prevention of the post-injection swelling, not in the treatment of malar edema [19]. Furthermore, in 2022, Siperstein proposed triamcinolone for the treatment of mild-long term or delayed onset swelling in a dose of 0.1 mL of 2.5 mg/mL triamcinolone with a cannula in each area [20]. Nonetheless, the author suggests triamcinolone being effective only for 2-6 weeks before the edema returns. In our analysis, the patients did not improve after the previous treatment with hyaluronidase nonetheless, all responded to the triamcinolone alone which proved to be effective for the period of 12 weeks at the follow-up.

According to our observations, injection with triamcinolone is a safe and effective option for the management of malar edema following hyaluronic acid filler injection. Nonetheless, further research with larger patient groups is needed to validate our results and to establish the most effective and safe concentration of triamcinolone injection.

References


Dermatology Quality of Life and Depression, Anxiety, and Stress Scale-42 in Scabies Patients

Serap Köran Karadoğan¹, Berna Ulgen Altay²

¹ Izmir Metropolitan Municipality Esrefpasa Hospital, Konak/Izmir, Turkey
² Department of Dermatology, Izmir Democracy University Medical Faculty, Buca Seyfi Demirsoy Training and Research Hospital, Konak/Izmir, Turkey

Key words: Scabies, quality of life, depression, anxiety, stress

Citation: Karadoğan SK, Ulgen Altay B. Dermatology Quality of Life and Depression Anxiety and Stress-42 Scale in Scabies Patients. Dermatol Pract Concept. 2024;14(2):e2024112. DOI: https://doi.org/10.5826/dpc.1402a112

Accepted: November 12, 2023; Published: April 2024

Copyright: ©2024 Karadoğan et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: Both the authors have contributed significantly to this publication.

Corresponding Author: Serap Körn Karadoğan, Izmir Metropolitan Municipality Esrefpasa Hospital Deparatment of Dermatology, Gaziler Street, No:315, 35170, Konak/Izmir, Turkey Email address: gafkaradogan@yahoo.com

ABSTRACT

Introduction: Scabies is a pruritic skin infestation with a globally increasing prevalence. Sleep problems and impaired social and personal interactions, mainly due to itching, have been reported.

Objectives: We aimed to determine the influence of scabies on quality of life and psychosocial health using Dermatology Life Quality Index (DLQI) and Depression Anxiety and Stress Scale-42 (DASS-42) and analyze whether there is a correlation between the two scales and any sociodemographic and clinical characteristic.

Methods: Scabies patients (>16 years) who presented to our outpatient clinics were enrolled. Age, sex, occupation, marital status, and education level and clinical features were recorded. DLQI and DASS-42 were used. Possible influence of demographic and clinical characteristics on total scores were analyzed. The Spearman coefficient analysis was performed to determine whether there is a correlation between these scores.

Results: Of 92 patients (mean age: 37.76±15.355, Female/Male: 1.09/1), 63% were married and 35.9% were high-school graduates; 27.2% and 23.9% were housewives and officers, respectively. Disease was generalized in 57.6% and duration of disease was mostly <4 weeks. Mean DLQI and DASS-42 scores were 13.16±7.638 and 42.10±30.644, respectively. Symptoms/feelings were affected predominantly. DLQI was affected ‘severely’ in 41.3% of patients.

Conclusions: Impairment of DLQI is a significant predictive parameter for higher DASS levels. Scabies is not only associated with impairment in DLQI but may also lead to psychosocial problems. All scabies patients should be evaluated and consulted—if needed—for possible problems of psychosocial status, including depression, anxiety, and stress, as well as clinical symptoms and secondary complications.
Introduction

Scabies is a pruritic skin infestation caused by an ectoparasite *Sarcoptes scabiei var. hominis* presenting with itchy lesions characteristically located on the web spaces of fingers, volar surfaces of wrists, inner thighs, umbilicus, areolae in women, and genitalia in men. Prolonged skin contact, usually more than 10 minutes, particularly among family members and/or sexual partners, is the most common mode of transmission. Handshakes, hugging, and casual touching are very rare modes of transmission. Diagnosis is usually made clinically. Dermoscopic and/or microscopic evaluation to detect feces, eggs, or even mites may be used to confirm the diagnosis [1,2].

The disease has been reported to cause 71 disability-adjusted life years (DALY)/100,000 people, contributing to 0.21% DALYs from all of the 315 conditions studied by the Global Burden of Disease in 2015 worldwide [2]. The protective skin barrier may be impaired due to severe pruritus, and secondary cutaneous bacterial infections and even some life-threatening conditions, including renal and cardiac diseases, have been reported particularly among immunocompromised patients [3]. Scabies not only causes pruritus and cutaneous signs but may also lead to impairment in the quality of life (QOL) of patients and even lead to social and psychological problems. Insomnia, a decrease in the quality of sleep, and negative influence on daily activities due to pruritus have been reported. Patients cannot go to work or school, may be stigmatized or excluded, or may face communication problems with friends and/or partners throughout the therapy period due both to the symptoms and to therapeutic methods including topicalointments with an unpleasant odor [3-4].

Dermatology Life Quality Index (DLQI) has increasingly been used in many dermatological conditions recently. It gives very important data both to predict the therapeutic results and the prognosis of the dermatoses [5]. The Depression, Anxiety and Stress Scale-42 (DASS-42) is a scale measuring three subscales–depression, anxiety and stress–both dimensionally and categorically and discriminates each in the same questionnaire [6]. DASS-42 or its shorter version (DASS-21) have previously been used in a few dermatoses, including oral lichen planus, eczema, and atopic dermatitis, as well as in specific populations such as employees, dermatologists, secondary school girls, and adolescent refugees [7-16].

There are only three studies investigating the relationship between QOL and psychological status of scabies patients using various scales, including Beck’s Depression Scale (BDS), Beck’s Anxiety Inventory (BAI), Hamilton Anxiety Rating Scale (HAM-A), Zung Self-Rating Depression Scale (SDS), and Zung Self-Reporting Anxiety Scale (SAS) [17-20]. In this study, we aimed to investigate the psychological burden of this disease using DASS-42 Scale and its possible correlation with DLQI results and also to determine whether any sociodemographic and clinical characteristics of the patients are related with these results.

Methods

We conducted a prospective and descriptive survey study after obtaining ethical clearance from the local ethics committee. All the patients who presented to our dermatology outpatient clinics between January and June 2023, aged ≥16 years, capable of writing, reading, and understanding a given questionnaire, and diagnosed as having scabies clinically and/or dermoscopically were enrolled. The exclusion criteria were pregnancy/lactation, any doubt about the clinical diagnosis, atypical forms of scabies (Norwegian Gale), being <16 years, chronic dermatological and systemic diseases (diabetes, hypertension, asthma, epilepsy, acne and psoriasis), or using any mood-altering drugs.

Patients’ age, sex, education level, marital status, occupation, and clinical characteristics such as distribution of lesions and duration of symptoms were recorded. The disease was categorized as ‘localized’ if lesions were located on <3 regions and ‘generalized’ if lesions were located on ≥3 regions.

After an informed consent form was signed by the patients and sociodemographic parameters were recorded, the patients were asked to complete the questionnaires of the Dermatology Life Quality Index (DLQI) and the Depression Anxiety and Stress Scale-42 (DASS-42).

DLQI was first developed by Finlay et al. as a questionnaire consisting of 10 items; it has been validated in more than 40 dermatological disease [5]. We used the validated Turkish version of this index [21]. There are 10 questions about the patient’s symptoms/feelings (questions 1–2), daily activities (questions 3–4), leisure and sports activities (questions 5–6), work and/or school (question 7), personal interactions (questions 8–9), and therapeutic challenges (question 10). The patient is asked to choose one of the 4 or 5 answers for every question. The answers are categorized as follows: very much-3, much-2, little-1, not much-0, not relevant-0, and unanswered question-0. All the points are summed, and a total score ranging from 0 and 30 is achieved. The higher the score, the more the patient’s quality of life (DLQI) is impaired. The range of scores are categorized as follows: 0–1= DLQI is not affected, 2–5= DLQI is mildly affected, 6–10= DLQI is moderately affected, 11–20=DLQI is severely affected, and 21–30=DLQI is very severely affected.
The DASS-42 is a 42-item questionnaire consisting of three subscales within 14 items, and a Likert-type evaluation is made (0=never, 1=sometimes, 2=very often, 3=always). It is an easy, short self-report questionnaire designed to evaluate the presence and severity of depression, anxiety, and stress in patients ≥ 16 years of age [6]. The patients are asked to reply to the questions considering the previous week. The total score is achieved after summing all the scores. Normal range is 0–9 for depression, 0–7 for anxiety, and 0–14 for stress. We used the Turkish version of the scale, which was modified slightly for the Turkish population [22].

Sample and Sample Size
Sample size was determined using PASS (NCSS Corp. Released 2011. Power Analyzes Sample Size for Windows, Version 11.0. Utah, USA) Pocket Programme. The average score of DLQI in the reference trial is 14.5±4.5. A sample size of 91 achieves 90% power to detect a difference of -1.6 between the null hypothesis mean of 15.0 and the alternative hypothesis mean of 16.5, with an estimated standard deviation of 4.5 and with a significance level (alpha) of 0.05000 using a two-sided one-sample t-test.

Statistical Methods
Collected data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp, Armonk, NY). Frequency and percentages for categorical data, and mean, standard deviation, median, and minimum and maximum descriptive values were used for continuous data. Kolmogorov-Smirnov Test was used to analyze normality test of data. The independent samples t-test for comparison of two groups with normal distribution, the Mann Whitney-U test for comparison of two groups without normal distribution, the ANOVA Test for comparison of more than two groups with normal distribution, and the Kruskal-Wallis H test for comparison of more than two groups without normal distribution were used. In the comparison of categorical variables, Fisher’s exact test or the chi-squared test, and Pearson or Spearman’s correlation test in determination of interaction between scale scores were used. Level of significance was set at $P<0.05$.

Results
Ninety-two patients were enrolled in the study. The median age of participants was 36 years (min-max, 18-84 years), with a slight predominance of females (n=48, 52.2%). The majority of the patients were aged between 16 and 35 years (48.9%), and 63% of the patients were married. The patients were mostly high school (35.9%, n=33) and university graduates (22.8%, n=21). Housewives and officers were the largest groups (27.2%, n=25 and 23.9%, n=22, respectively) (Table 1).

Generalized disease was noted more than localized disease (57.6% vs 42.4%, respectively). Duration of the disease was mostly less than four weeks (46.7%) (Table 2). The mean DLQI was 13.16±7.638. DLQI was ‘affected severely’ in 41.3% (n=38) of patients. The most affected domain of DLQI was symptoms/feelings (mean 3.89±1.593), followed by difficulties at work/school (mean 2.25±2.058). The mean±SD of the total DASS score was 42.10±30.644 (with subgroups of depression 13.11±11.595, anxiety 12.13±9, and stress 16.95±11.291) (Table 3).

Although not statistically significant, DLQI was affected more in patients >55 years, males (13.68±7.172), singles (13.47±6.934), officers (14.91±6.921), and those with higher education level (14.21±7.749) in comparison to other groups of age, sex, occupation, and education.

Table 1. Demographic characteristics of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-35</td>
<td>45</td>
<td>48.9</td>
</tr>
<tr>
<td>36-55</td>
<td>29</td>
<td>31.5</td>
</tr>
<tr>
<td>≥55</td>
<td>18</td>
<td>19.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
<td>47.8</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>52.2</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Married</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>22</td>
<td>23.9</td>
</tr>
<tr>
<td>Student</td>
<td>9</td>
<td>9.8</td>
</tr>
<tr>
<td>Worker</td>
<td>17</td>
<td>18.5</td>
</tr>
<tr>
<td>Housewife</td>
<td>25</td>
<td>27.2</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>20.7</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lit.- primary</td>
<td>19</td>
<td>20.7</td>
</tr>
<tr>
<td>Middle</td>
<td>19</td>
<td>20.7</td>
</tr>
<tr>
<td>High</td>
<td>33</td>
<td>35.9</td>
</tr>
<tr>
<td>University</td>
<td>21</td>
<td>22.8</td>
</tr>
</tbody>
</table>

Table 2. Clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>53</td>
<td>57.6</td>
</tr>
<tr>
<td>Localized</td>
<td>39</td>
<td>42.4</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>21</td>
<td>22.8</td>
</tr>
<tr>
<td>4-12 weeks</td>
<td>28</td>
<td>30.4</td>
</tr>
<tr>
<td>&lt;4 weeks</td>
<td>43</td>
<td>46.7</td>
</tr>
</tbody>
</table>
Table 3. Statistics of total and subgroups of DASS-42 and domains and subgroups of DLQI.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DASS-42</strong></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42.10±30.644</td>
</tr>
<tr>
<td>Depression</td>
<td>13.11±11.595</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12.13±9.216</td>
</tr>
<tr>
<td>Stress</td>
<td>16.95±11.291</td>
</tr>
<tr>
<td><strong>DLQI (domains)</strong></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13.16±7.638</td>
</tr>
<tr>
<td>Symptoms and feelings</td>
<td>3.89±1.593</td>
</tr>
<tr>
<td>Daily activities</td>
<td>2.09±1.954</td>
</tr>
<tr>
<td>Leisure</td>
<td>1.98±1.898</td>
</tr>
<tr>
<td>Relationships</td>
<td>1.64±1.289</td>
</tr>
<tr>
<td>Work-school</td>
<td>2.25±2.058</td>
</tr>
<tr>
<td>Therapeutic challenge</td>
<td>1.32±1.119</td>
</tr>
<tr>
<td><strong>DLQI (subgroups)</strong></td>
<td>n (%)</td>
</tr>
<tr>
<td>Very severely affected</td>
<td>18 (19.6)</td>
</tr>
<tr>
<td>Severely affected</td>
<td>38 (41.3)</td>
</tr>
<tr>
<td>Moderately affected</td>
<td>18 (19.6)</td>
</tr>
<tr>
<td>Mildly affected</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>Unaffected</td>
<td>5 (5.4)</td>
</tr>
</tbody>
</table>

levels. On the other hand, it was found that DLQI was significantly affected in patients with general involvement (16.06±7.159) and >12 weeks of duration (17.81±7.012) (P<0.05) (Table 4).

For total DASS-42 score, depression, anxiety, and stress levels were significantly higher in patients >55 years (P<0.035), patients with generalized involvement (P<0.001), and patients with a duration of >12 weeks (P<0.001), respectively. However, no significant difference was observed among other demographic and clinical characteristics, including sex, marital status, occupation, and education level (Table 5).

DLQI of patients were mostly affected severely (median 42) and very severely (median 77). DLQI of patients who experienced very severe depression (15.2%), anxiety (17.4%), and stress (12%) were affected very severely (64.3%, 50%, and 63.6%, respectively) (Table 6).

Patients with very severe depression, anxiety, and stress had higher scores of DLQI in comparison with other groups (21.43±4.735, 18.88±7.710 and 21.91±5.088, respectively) (Table 7).

Spearman correlation coefficient analysis revealed a positive and significant correlation between total DLQI score and total (r=0.582) and subgroups of DASS-42 (depression (r=0.618), anxiety (r=0.508), and stress level (r=0.553) scores, respectively) (P<0.001) (Table 8).

Discussion

Scabies is a pruritic and contagious dermatosis which has been reported to have affected 2.8% of the population in the year 2015. A total increase of 6.6% in the incidence of scabies between the years of 2005-2015 has been estimated [24]. In a recent study, it was emphasized that movements of people, including tourists and immigrants in Croatia, may have had a possible influence on scabies movements [25]. An approximate 30-fold increase in prevalence comparing the years 2017 and 2019 has been noted in our country [26]. Ural et al. reported that the COVID-19 pandemic period has also contributed [27]. We think this may have been even more prominent during recent months probably due to low socioeconomic level and poor hygiene conditions, which may have unfortunately worsened after the increasing number of immigrants and the earthquake in southeastern, leading to thousands of victims.

Skin diseases are important risk factors for emotional stress, acute anxiety, and mood disorders, sometimes even affecting the therapeutic response and course of the disease. Shabbaz et al. [28] demonstrated that QoL in patients with various dermatoses on exposed parts is impaired. The negative influence of both symptoms and therapeutic challenges on the quality of life of scabies patients and/or their family members has also been well-established [1, 3, 4, 17, 29].

The psychological burden of many dermatoses, including psoriasis, vitiligo, acne, atopic dermatitis, seborrheic dermatosis, psoriasis, eczema, hidradenitis suppurativa, oral lichen planus, alopecia, steroid-resistant dermatitis, and chronic pruritus, has been thoroughly investigated previously [7-11, 19, 23]. There are only three studies analyzing the correlation between DLQI and psychological consequences of scabies, in which DLQI and various psychometric, including BDS/ BAS, HAM-A and SAS/ SDS, were used [17, 18, 20]. Here, we investigated the impact of this disturbing disease on the patients’ psychological health using DASS-42 and analyzed its possible correlation with DLQI results.

Bilal et al. [1] stated that the feeling of embarrassment and shopping were the most affected domains in their male patients (58.9%). The domains affected predominantly were shopping, clothing, and work activities, which they concluded may reflect the young, active age group living in urban areas. In a study of 102 scabies patients, Nair et al. [3] concluded that scabies can affect DLQI in the form of work, sleep disturbances, and psychosocial problems both in patients and their family members. The most common age group was 21-40 years, with a predominance of students and housewives, and the major domain affected was work activity (74.2%), followed by feeling of embarrassment (64.5%). In another study of 120 scabies patients, difficulty at work was mostly experienced, followed by feelings of
factors influencing QoL, depression and anxiety of patients with skin diseases, and the correlation between the three using DLQI, and SAS, and SDS. They concluded that psoriasis, acne, atopic dermatitis, steroid-dependent dermatitis, and alopecia have a certain impact on QoL of most patients and may cause different degrees of anxiety and depression. Sun et al. [19] observed a strong correlation between skin diseases-neurodermatitis, eczema, and psoriasis and anxiety using HAM-A scale and concluded that the likelihood of anxiety decreases as age increases. Although we also found a similar positive correlation between scabies and DASS-42 scores, patients older than 55 years were significantly more affected and had higher DASS-42 scores in our study.

It is well established that certain populations including immunocompromised patients, children, the elderly, and patients with developmental disabilities have a higher risk of acquiring the disease and experiencing the complications. This may be attributed to the late onset of symptoms, particularly itching, leading to a delay in seeking medical care until the lesions are generalized since type 1 and delayed type 4 immune response, which normally develops in weeks 1–4 after infestation, may be impaired in these patients [2]. Indeed, it is postulated that the stress surrounding COVID-19 and embarrassment and social relationships. The patients were aged mostly 18–30 years [4]. Similarly, in the present study, the majority of the patients were aged between 16 and 35 years (48.9%), with a predominance of housewives and officers, and the most affected domain was symptoms and feelings (mean: 3.89±1.593), followed by difficulties at work and school (mean 2.25±0.205).

The mean DLQI score of our study population was 13.16±7.638. This value was in concordance with the previous studies of DLQI in scabies, which reported mean DLQI values of between 10.09 and 14.95±4.5 [1, 17, 30]. There have been studies reporting a small-to-moderate effect of scabies on DLQI [3, 30, 32-34]. On the other hand, in one study, DLQI in 72.2% of patients was moderate-to-extremely affected. DLQI was ‘affected severely’ in 41.3% (n=38) of our patients, similar to most of the previous studies [1,17]. A mild effect was reported only in one study performed in rural areas, and the authors concluded that this may be attributable to the fact that the QoL is so poor that people do not consider scabies as a problem at all [32].

The mean±SD DASS-42 score in our study was 42.10±30.644 (depression 13.11±11.595, anxiety 12.13±9.216, and stress 16.95±11.291). Guo et al. [23] investigated the

---

### Table 4. Distribution of demographic and clinical characteristics according to means of DLQI.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>n (%)</th>
<th>DLQI Mean±SD</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>16-35</td>
<td>45 (48.9)</td>
<td>13.76±7.517</td>
<td>0.473</td>
</tr>
<tr>
<td></td>
<td>36-55</td>
<td>29 (31.5)</td>
<td>11.72±8.293</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;55</td>
<td>18 (19.6)</td>
<td>14±6.894</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>44 (47.8)</td>
<td>13.68±7.172</td>
<td>0.536</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>48 (52.2)</td>
<td>12.69±8.088</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>Single</td>
<td>34 (37)</td>
<td>13.47±6.934</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>58 (63)</td>
<td>12.98±8.075</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>Officer</td>
<td>22 (23.9)</td>
<td>14.91±6.921</td>
<td>0.651</td>
</tr>
<tr>
<td></td>
<td>Student</td>
<td>9 (9.8)</td>
<td>11.22±6.723</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worker</td>
<td>17 (18.5)</td>
<td>12.29±7.769</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Housewife</td>
<td>25 (27.2)</td>
<td>12.28±8.106</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>19 (20.7)</td>
<td>14±8.731</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td>Lit.-Primary</td>
<td>19 (20.7)</td>
<td>13.16±8.995</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>19 (20.7)</td>
<td>11.53±6.266</td>
<td>0.688</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>33 (35.9)</td>
<td>14.21±7.749</td>
<td></td>
</tr>
<tr>
<td></td>
<td>University</td>
<td>21 (22.8)</td>
<td>13±7.537</td>
<td></td>
</tr>
<tr>
<td>Involvement</td>
<td>Generalized</td>
<td>53 (57.6)</td>
<td>16.06±7.159</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>39 (42.4)</td>
<td>9.23±6.483</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>&gt;12 weeks</td>
<td>21 (22.8)</td>
<td>17.81±7.012</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-12 weeks</td>
<td>28 (30.4)</td>
<td>13.29±7.049</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>&lt;4 weeks</td>
<td>43 (46.7)</td>
<td>10.81±7.388</td>
<td></td>
</tr>
</tbody>
</table>

Original Article | Dermatol Pract Concept. 2024;14(2):e2024112
social isolation can have negative effects on mental stress in older people. Psychological stress has an impact on many skin diseases and can play a substantial role in exacerbating disease activity [31].

There are various studies on the demographic characteristics of patients with dermatoses and DLQI scores. Shahbaz et al. [28] reported a relation between sex, marital status, and duration of disease and DLQI in most dermatoses on exposed parts, including acne, hirsutism, melasma, vitiligo, and eczema. Yıldırım et al. [17] found no relationship between BDS/BAS and age, sex, education level, and duration of scabies. Similarly, Bilal et al. [1] reported a large effect of scabies on DLQI without any significant association with sociodemographic characteristics, including

Table 5. Distribution of demographic characteristics according to total and subgroups of DASS-42 Score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
<th>Total DASS</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55</td>
<td>18</td>
<td>19.6</td>
<td>50.06±34.374</td>
<td>16.78±12.941</td>
<td>13.83±9.691</td>
<td>19.44±12.858</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>0.035</td>
<td>0.039</td>
<td>0.045</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44</td>
<td>47.8</td>
<td>38.61±32.407</td>
<td>12.20±12.320</td>
<td>10.48±9.586</td>
<td>16.16±12.069</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>52.2</td>
<td>45.29±28.905</td>
<td>13.94±10.953</td>
<td>13.65±8.687</td>
<td>17.67±10.604</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>0.229</td>
<td>0.477</td>
<td>0.100</td>
<td>0.525</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>58</td>
<td>63</td>
<td>38.26±28.651</td>
<td>11.84±10.780</td>
<td>10.69±8.285</td>
<td>15.69±10.795</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>0.117</td>
<td>0.173</td>
<td>0.052</td>
<td>0.165</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Officer</td>
<td>22</td>
<td>23.9</td>
<td>35.05±21.588</td>
<td>10.27±8.419</td>
<td>9.32±6.121</td>
<td>15.36±9.016</td>
</tr>
<tr>
<td>Student</td>
<td>9</td>
<td>9.8</td>
<td>57.00±41.728</td>
<td>18.44±16.569</td>
<td>16.67±13.416</td>
<td>23.00±13.711</td>
</tr>
<tr>
<td>Worker</td>
<td>17</td>
<td>18.5</td>
<td>38.41±29.424</td>
<td>11.76±10.651</td>
<td>11.47±8.449</td>
<td>15.18±11.706</td>
</tr>
<tr>
<td>Housewife</td>
<td>25</td>
<td>27.2</td>
<td>46.64±29.627</td>
<td>14.36±11.324</td>
<td>14.44±8.996</td>
<td>17.84±10.617</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>20.7</td>
<td>40.53±33.692</td>
<td>13.42±13.234</td>
<td>10.79±10.228</td>
<td>16.32±12.966</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>0.393</td>
<td>0.447</td>
<td>0.178</td>
<td>0.462</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lit-primary</td>
<td>19</td>
<td>20.7</td>
<td>48.26±32.844</td>
<td>15.95±12.376</td>
<td>13.68±9.621</td>
<td>18.63±11.781</td>
</tr>
<tr>
<td>Middle</td>
<td>19</td>
<td>20.7</td>
<td>31.58±24.885</td>
<td>9.26±8.491</td>
<td>9.53±7.479</td>
<td>12.79±10.003</td>
</tr>
<tr>
<td>High</td>
<td>33</td>
<td>35.9</td>
<td>47.30±34.645</td>
<td>14.91±13.347</td>
<td>14.18±10.510</td>
<td>18.21±12.328</td>
</tr>
<tr>
<td>University</td>
<td>21</td>
<td>22.8</td>
<td>37.86±24.882</td>
<td>11.19±9.647</td>
<td>9.86±7.411</td>
<td>17.19±10.003</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>0.23</td>
<td>0.20</td>
<td>0.17</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>53</td>
<td>57.6</td>
<td>58.62±27.093</td>
<td>18.64±11.016</td>
<td>17.06±8.570</td>
<td>23.08±9.579</td>
</tr>
<tr>
<td>Localized</td>
<td>39</td>
<td>42.4</td>
<td>19.64±18.596</td>
<td>5.59±7.429</td>
<td>5.44±8.800</td>
<td>8.62±7.489</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>21</td>
<td>22.8</td>
<td>64.33±31.614</td>
<td>21.33±11.573</td>
<td>18.76±10.554</td>
<td>24.24±10.881</td>
</tr>
<tr>
<td>4-12 weeks</td>
<td>28</td>
<td>30.4</td>
<td>51.29±31.037</td>
<td>17.25±12.447</td>
<td>13.93±8.726</td>
<td>20.39±11.519</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>92</td>
<td>100</td>
<td>42.10±30.644</td>
<td>13.11±11.595</td>
<td>12.13±9.216</td>
<td>16.95±11.291</td>
</tr>
</tbody>
</table>
environmental cleaning, may have contributed to the extraordinary impairment of DLQI in the elderly. Although there is limited evidence concerning the relation between duration of disease and DLQI in scabies patients, eight weeks of disease has been reported to influence the DLQI and burden of the disease in two studies [17, 31]. Although most of our patients had a duration less than four weeks, we observed a significant difference of DLQI in patients with longer duration. Patients with generalized disease and longer duration usually have more pruritus and secondary skin changes, including excoriations and cutaneous infections, possibly explain the greater impairment of DLQI.

For total DASS-42 score, depression, anxiety, and stress levels were significantly higher in patients > 55 years (P=0.035), with generalized involvement (P<0.001), and age group, education level, and occupation. In the present study, although not significant statistically, DLQI was affected more in patients > 55 years, males (13.68±7.172), singles (13.47±6.934), officers (14.91±6.921), and those with higher education level (14.21±7.749) in comparison with other groups of age, sex, occupation, and education level. On the other hand, it was found that DLQI was significantly affected in patients with generalized involvement (16.06±7.159) and >12 weeks of duration (17.81±7.012) (P<0.05). Since older patients constituted a small group in our population, it is worth observing the greater impairment of DLQI in these patients. Increased and prolonged social isolation during the whole COVID-19 pandemic in addition to the unpleasant and impractical topical therapy of scabies, including long hours of ointments and self- and environmental cleaning, may have contributed to the extraordinary impairment of DLQI in the elderly.

Although there is limited evidence concerning the relation between duration of disease and DLQI in scabies patients, eight weeks of disease has been reported to influence the DLQI and burden of the disease in two studies [17, 31]. Although most of our patients had a duration less than four weeks, we observed a significant difference of DLQI in patients with longer duration. Patients with generalized disease and longer duration usually have more pruritus and secondary skin changes, including excoriations and cutaneous infections, possibly explain the greater impairment of DLQI.

For total DASS-42 score, depression, anxiety, and stress levels were significantly higher in patients > 55 years (P=0.035), with generalized involvement (P<0.001), and

Table 6. Distribution of subgroups of DLQI and DASS-42.

<table>
<thead>
<tr>
<th>Variable</th>
<th>DASS-42</th>
<th>Median (Min-Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>Mildly affected</td>
<td>Severe affected</td>
</tr>
<tr>
<td>DLQI</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>92 (100)</td>
<td>10</td>
</tr>
<tr>
<td>Depression</td>
<td>14 (15.2)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>10 (10.9)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (10.9)</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>46 (50)</td>
<td>5 (10.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16 (17.4)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>20 (21.7)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (15.2)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Mild</td>
<td>9 (9.8)</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>33 (35.9)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Stress</td>
<td>11 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>14 (15.2)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (15.2)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Mild</td>
<td>11 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>42 (45.7)</td>
<td>4 (9.5)</td>
</tr>
</tbody>
</table>

Table 7. Mean DLQI scores according to subgroups of DASS-42.

<table>
<thead>
<tr>
<th>Variable</th>
<th>DASS-42</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very severe</strong></td>
<td><strong>Severe</strong></td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td>DLQI (total score)</td>
<td>Depression</td>
<td>21.43±4.735</td>
</tr>
<tr>
<td>Anxiety</td>
<td>18.88±7.710</td>
<td>15.40±6.303</td>
</tr>
<tr>
<td>Stress</td>
<td>21.91±5.088</td>
<td>15.07±6.719</td>
</tr>
</tbody>
</table>
with duration of >12 weeks (P<0.001) in comparison with other age, involvement, and duration groups, respectively. However, no significant difference was observed among other demographic and clinical characteristics (sex, marital status, occupation, and education level). Although the mean duration of disease was predominantly <4 weeks, we observed that patients with >12 weeks of duration tended to have higher levels of depression, anxiety, and stress. In a recent cross-sectional study with a much longer mean duration of symptoms (5.9 months) than all previous studies and ours, scabies patients had more anxiety, depression, and impaired QoL and tended to have moderate-to-severe depression in comparison to controls [20].

DLQI of patients was mostly affected severely (median 42) and very severely (median 77). DLQI of patients with very severe depression (15.2%), anxiety (17.4%), and stress (12%) were affected very severely (64.3%, 50%, and 63.6%, respectively) and had higher scores of DLQI (21.43±4.735, 18.88±7.710, and 21.91±5.088, respectively). Spearman correlation coefficient analysis revealed a positive and significant correlation between total DLQI score and total DASS-42 (r =0.582), anxiety (r =0.508), and stress level (r =0.553) scores, respectively (P<0.001). All these findings suggest that the more DLQI is impaired, the higher the level of depression, anxiety, and stress in scabies patients.

The limitations of our study are the small size of the population and the lack of a control group and pediatric patients.

**Conclusion**

We conclude that impairment of DLQI is a statistically significant predictive parameter for an increase in depression, anxiety, and stress levels. DASS-42 score is an important variable affecting the DLQI independently from other demographic and clinical characteristics of scabies patients. Scabies is not only associated with impairment in quality of life, but it also may lead to psychosocial problems. All scabies patients should be evaluated and consulted, if needed, for possible problems of psychosocial life, including depression, anxiety, and stress, as well as clinical symptoms and other secondary complications.

**Table 8. Spearman rho analysis demonstrating the relationship between DLQI and DASS-42 (total and subgroups).**

| DLQI | Correlation coefficient | P **
---|---|---
DASS-42 Total | .582** | .000
Depression | .618** | .000
Anxiety | .508** | .000
Stress | .553** | .000
DLQI | 1.000 | .000

** Correlation is significant at the 0.01 level (2-tailed).

References


Original Article | Dermatol Pract Concept. 2024;14(2):e2024112


Impact of Vitiligo on Quality of Life in Patients of Skin of Color and Its Correlation With Clinical Severity Assessment Scores Utilizing Disease Specific Scores: A Cross-Sectional Study

Guneet Awal¹, Navleen Kaur¹, Guramrit Singh¹, Nishant Sharma²

¹ Department of Dermatology, Venereology and Leprosy, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, India
² Department of Community Medicine, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, India

Key words: vitiligo, quality of life, skin of color, VIS-22, VitiQoL


Accepted: October 18, 2023; Published: April 2024

Copyright: ©2024 Awal et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Dr. Guneet Awal, 469, East Mohan Nagar, Opp. DSP Park, Amritsar, Punjab 143001. Phone numbers- 998834379, 9115703086 E-mail: guneetawal@gmail.com

ABSTRACT

Introduction: Assessment of disease severity of vitiligo is exigent as it is a psychosomatic ailment. VIDA (vitiligo disease activity score) and VASI (vitiligo area severity index) were previously used for this evaluation. Recently, the introduction of two vitiligo specific tools, vitiligo impact scale (VIS)-22 and Vitiligo Quality of Life Index (VitiQoL) has aided in assessing the quality of life (QOL) in a pertinent manner.

Objectives: To measure the QOL in vitiligo using disease specific indices (VitiQoL and VIS-22), to assess their relationship with disease severity (VASI and VIDA) and to determine the correlation between QOL scores (VIS-22 and VitiQoL).

Methods: This observational cross-sectional study included 195 patients with vitiligo, and their disease severity was calculated using VASI and VIDA scoring. Patients were asked to fill questionnaires for assessing the QOL using validated tools i.e. VIS-22 and VitiQoL.

Results: Significant correlation was demonstrated between both QOL scores and VASI score (P value 0.001) with slightly higher values for VitiQoL (r = 0.824) than with VIS 22 (r = 0.693). Both scores exhibited a significant association with VIDA score (P value < 0.001). Moreover, statistically significant correlation was found between VIS-22 and VitiQoL, thereby proving the concordance between these scores.

Conclusions: The study infers that QOL seemed to be remarkably dependent on the clinical severity scores and that higher disease activity corresponds to poorer QOL. It is imperative to precisely assess burden of vitiligo and the impairments caused by it in order to aid multi-modality management and allow more standardized research.
Introduction

Vitiligo, a pigmentary disorder with loss of melanocytes, although predominantly asymptomatic, is a cause of great cosmetic and psychological concern [1]. There is an increasing prevalence of vitiligo affecting up to 1%-4% of the world population. In India, vitiligo has been known as “sweta kustha,” which translates as “white leprosy”[2]. Individuals with vitiligo may be treated with stigma due to false belief of having Hansen disease, which can be acquired by contact, thereby causing low self-esteem, poor body image and depression [3]. They face difficulty in finding jobs and getting married as a result of social discrimination and cultural beliefs, leading to anxiety and distress.

Vitiligo can be classified as a psychosomatic ailment, with both psychological and physical elements contributing to disease development, relapses and remissions [4]. Assessment of disease severity is imperative since it affects patients psychological well-being. Vitiligo Area Scoring Index (VASI) is a quantitative score given by Hamzavi et al in which hand units are used to calculate percentage of vitiligo involvement [5]. Vitiligo disease activity score (VIDA) is another assessment tool which is based on subjective assessment of disease activity [6].

Earlier there was no specific quality of life (QOL) assessment tool for vitiligo and it was measured by using nonspecific tools such as Dermatology Life Quality Index (DLQI), Skindex-26 and SF-36 [2,7-9]. However, it is increasingly recognized that vitiligo has a greater impact on QOL owing to psychological concerns such as lack of self-confidence, unfavorable body views, and failed social interactions, rather than physical problems [7,8,10,11]. Hence, two vitiligo specific tools have been developed, which are Vitiligo impact scale (VIS)-22 and Vitiligo Quality Of Life index (VitiQoL) [12,13]. VitiQoL is an objective, vitiligo specific measure of disease status, burden and treatment outcome for patients. It is substantiated using disease-specific items from in-depth open-ended patient interviews, clinical input and literature review [14]. Similarly, VIS-22, another disease-specific questionnaire, consists of 22 easily understandable questions: 19, common to all patients and one each for patients who are married, unmarried, working, or studying.

Objectives

In this article we have assessed and analyzed the QOL of vitiligo patients using disease specific indices, and its relationship with clinico-demographic patterns and severity of vitiligo as there is paucity of data on their correlation in Indian patients.

Methods

Study Site and Population

A total of 195 clinically diagnosed patients of vitiligo attending the dermatology department of a tertiary care hospital were included in this cross-sectional, questionnaire-based study after obtaining informed consent.

Study Period

It was conducted over a period of 2 years from August 2019 to July 2021.

Inclusion Criteria

All consenting patients aged ≥18 years with clinical diagnosis of vitiligo were included.

Exclusion Criteria

Patients less than 18 years of age or with other disorders and disabilities associated with social stigma.

Study Procedure

Demographic details including the patients name, age, sex, occupation, marital status, duration, onset and progression of the disease were recorded. Patients were diagnosed clinically and the findings were corroborated with dermoscopy. The severity of disease was calculated by using VASI and VIDA scoring and their correlation with VIS-22 and VitiQoL scores was evaluated.

Study Measurement Tools

VASI score is a quantitative severity evaluation score that is evaluated in the same way as the Psoriasis Area and Severity Index (PASI) score. The magnitude of residual depigmentation is indicated as: 100%-depigmented area exceeds the pigmented area; 50%-depigmented and pigmented areas are equal; 25%-pigmented area exceeds the depigmented area; and 10%-specks of depigmentation are present [5]. Each body site (Hands, upper extremities, trunk, lower extremities and feet) VASI is calculated. The cumulative body VASI is determined as (range of 0-100):

\[
\text{VASI} = \sum (\text{all body sites}) \times (\text{residual depigmentation})
\]

Njoo et al utilized the VIDA score for the first time in 1999 [6]. It is a six-point scale based on patient perception of disease activity over time and is graded as follows-VIDA score + 4: activity lasting 6 weeks or less; score +3: activity lasting 6 weeks to 3 months; score 2: activity lasting 3-6 months; score1: activity lasting 6-12 months; score 0: stable for 1 year or more; score -1: stable with spontaneous
re-pigmentation for 1 year or more. A low Vitiligo disease activity score indicates less vitiligo activity.

Lilly et al in 2013 proposed VitiQoL, which is a disease specific instrument based on three factors: stigma, participation limitation and behavior [14]. It comprises of 15 questions with a seven-point Likert scale (0-6) and the total scores ranging from 0 to 90. Individuals with higher scores indicate a poorer QOL.

VIS-22, the modified version of VIS, comprises of 22 items encompassing areas of self-confidence, anxiety, depression, marriage, family worries, social interactions, school/college related, occupation related, treatment related and attitude. Individual responses were scored from 0 to 3; a higher score denoting worse QOL [12,15]. Gupta et al graded the VIS-22 scores as: 0-5: no impact; 6-15: mild impact; 16-25: moderate impact; 26-40: large impact and 41-66: very large impact [16].

Ethical clearance for the study was obtained from the Institutional Ethics committee. Required permissions were obtained before the use of these assessment scores for the present study. The patients were asked to fill the questionnaires to assess the QOL using validated tools i.e VIS-22 and VitiQoL. A bilingual dermatologist translated the English versions of both the questionnaires into Punjabi language. Backward translations were done by a different bilingual dermatologist. The validity of translations was cross-checked by the evaluators.

Statistical Analysis
Data was analyzed using Statistical Package for the Social Sciences version 26 software (SPSS Inc.). Qualitative data were described using number and percentages. Descriptive statistics, mean and SD were calculated for quantitative variables. For assessment of correlation between QOL and vitiligo severity scores, Pearson correlation coefficient was used. For comparison of demographic profile, independent t test and analysis of variance (ANOVA) test was used. Probability value (P value) of less than 0.05 was considered significant. Intra class correlation coefficient was used to find agreement between the two quality of life scores.

Results
A total of 195 patients were recruited in the study. The mean age was 35.64 ± 14.76 years. Vitiligo was most commonly seen in patients aged 30 to 39 years (34.35%) with mean duration of 6.7 years and maximum (39.49%) patients presenting within 3 years of onset. Family history of a first-degree relative with vitiligo was positive in 34 patients (17.43%). Mostly, patients belonged to Fitzpatrick skin type 3 (39.48%) and 4 (51.28%). 115 patients were married whereas 72 were single and 8 divorced. The most common occupational group was laborer (40%) followed by student (18.5%), household worker (17.95%), semiskilled worker (13.84%), skilled worker (6.67%), and unemployed (3.04%). Both exposed and nonexposed sites were involved in 42.56%, only non-exposed sites in 36.4% and exposed sites in 21.02% patients. Of these, upper limbs constituted 24.1% followed by lower limbs (15.89%).

A maximum number of patients (27.17%) had VIDA score of +2, 24.61% of +3 whereas 15.38% had VIDA score of 0. The mean VASI score in this study was 22.63±8.06 and it was significantly associated with duration of disease (P < 0.05). There was significant association between VASI score and VIDA score, with highest VASI score in patients with a VIDA score of +4.

Overall, the mean VIS-22 score of our study population was 27.25±11.19, reflecting altogether a large impact on QOL with the mean score in females (27.76±11.86) being higher than males (26.91±10.82), though not statistically significant. Patients within age group 18-29 years and disease duration of 7-12 years had the highest VIS-22 score of 29.65±14.07 and 28.32±11.96 respectively. Skilled patients had the lowest VIS-22 score (23.15±9.51) while the household workers and laborers had higher VIS-22 scores (29.52±12.57 and 28.02±11.39 respectively). VIS-22 scores were higher among divorced patients (33.25±13.71), individuals with skin type V (29.11±12.7) and who had lesions on exposed parts of the body (27.92±11.31). The score was highest in patients with lesions on face (33.64±14.82) followed by chest (31.24±12.43) (Table 1).

Out of 195 patients, most patients had moderate impact (45.4%) and large impact (33.7%) with fewer having mild impact (8.6%) and very large impact (12.2%) in their QOL (Figure 1A). Maximum number (47%) of males had moderate impact on QOL with respect to VIS-22 scores whereas maximum number of females (49%) had large impact (Figure 1B).

Statistically significant strong correlation was observed between VIS-22 and VASI scores (r 0.693, P value < 0.001) as shown in Figure 2A. Overall, mean VASI scores were highest (25.91±11.84) in patients who had large impact followed by those who had moderate impact on their QOL (13.18±4.77) (Table 2). While ascertaining the strength of relationship between VIS-22 and VIDA score using Pearson correlation coefficient, a weak positive correlation was determined between these scores (P value=0.001) (Figure 2B).

The questions related to social interactions (3, 12 and 13) and anxiety (2,11) domains were the major contributors to VIS-22 scores in our study.

A higher VitiQoL score was seen in females (25.75±14.15) as compared to males (24.34±12.98) (P > 0.05). A significant association (P value< 0.05) was seen between VitiQoL scores and age of patient (18-29 years; 29.77±17.97) as well as
Table 1. Correlation of VIS-22 Score With Demographic Variables in patients of vitiligo

<table>
<thead>
<tr>
<th>VIS22</th>
<th>N</th>
<th>VIS22 mean</th>
<th>Standard deviation of VIS22</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>118</td>
<td>26.9153</td>
<td>10.82145</td>
<td>0.606</td>
</tr>
<tr>
<td>M</td>
<td>77</td>
<td>27.7662</td>
<td>11.86647</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>48</td>
<td>26.3958</td>
<td>11.58271</td>
<td>0.567</td>
</tr>
<tr>
<td>30-39</td>
<td>66</td>
<td>27.0000</td>
<td>9.78067</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>46</td>
<td>26.6739</td>
<td>10.46062</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>35</td>
<td>29.6571</td>
<td>14.07113</td>
<td></td>
</tr>
<tr>
<td>Duration of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>78</td>
<td>28.3205</td>
<td>11.96802</td>
<td>0.757</td>
</tr>
<tr>
<td>3-6</td>
<td>56</td>
<td>26.8214</td>
<td>11.13080</td>
<td></td>
</tr>
<tr>
<td>7-12</td>
<td>31</td>
<td>25.2581</td>
<td>9.67460</td>
<td></td>
</tr>
<tr>
<td>13-15</td>
<td>18</td>
<td>27.9444</td>
<td>12.52044</td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td>12</td>
<td>26.4167</td>
<td>8.94893</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>57</td>
<td>27.1930</td>
<td>10.22329</td>
<td>0.963</td>
</tr>
<tr>
<td>Negative</td>
<td>138</td>
<td>27.2754</td>
<td>11.64673</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorce</td>
<td>8</td>
<td>33.2500</td>
<td>13.70870</td>
<td>0.304</td>
</tr>
<tr>
<td>Single</td>
<td>70</td>
<td>27.1000</td>
<td>11.60104</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>117</td>
<td>26.9316</td>
<td>10.80128</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>35</td>
<td>27.0857</td>
<td>11.89259</td>
<td>0.388</td>
</tr>
<tr>
<td>Labour</td>
<td>78</td>
<td>28.0256</td>
<td>11.39603</td>
<td></td>
</tr>
<tr>
<td>Household worker</td>
<td>36</td>
<td>29.5278</td>
<td>12.75816</td>
<td></td>
</tr>
<tr>
<td>Semiskilled</td>
<td>27</td>
<td>24.7407</td>
<td>7.96914</td>
<td></td>
</tr>
<tr>
<td>Skilled</td>
<td>13</td>
<td>23.1538</td>
<td>9.51180</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>6</td>
<td>24.6667</td>
<td>10.30857</td>
<td></td>
</tr>
<tr>
<td>Skin type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>75</td>
<td>28.1333</td>
<td>11.71201</td>
<td>0.436</td>
</tr>
<tr>
<td>Type IV</td>
<td>103</td>
<td>26.3010</td>
<td>10.56338</td>
<td></td>
</tr>
<tr>
<td>Type V</td>
<td>17</td>
<td>29.1176</td>
<td>12.97537</td>
<td></td>
</tr>
<tr>
<td>Sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>41</td>
<td>27.9268</td>
<td>11.31457</td>
<td>0.977</td>
</tr>
<tr>
<td>Covered</td>
<td>70</td>
<td>26.2714</td>
<td>11.54440</td>
<td></td>
</tr>
<tr>
<td>Exposed+covered</td>
<td>84</td>
<td>27.3929</td>
<td>11.03883</td>
<td></td>
</tr>
<tr>
<td>Individual sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>7</td>
<td>22.8571</td>
<td>9.90671</td>
<td>0.065</td>
</tr>
<tr>
<td>Face</td>
<td>17</td>
<td>33.6471</td>
<td>14.82793</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>25</td>
<td>31.2400</td>
<td>12.43074</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>28</td>
<td>24.1429</td>
<td>7.88207</td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td>26</td>
<td>29.1154</td>
<td>11.76206</td>
<td></td>
</tr>
<tr>
<td>UL</td>
<td>47</td>
<td>25.7872</td>
<td>10.75808</td>
<td></td>
</tr>
<tr>
<td>LL</td>
<td>31</td>
<td>26.0645</td>
<td>9.81813</td>
<td></td>
</tr>
<tr>
<td>Genital</td>
<td>6</td>
<td>23.6667</td>
<td>7.22957</td>
<td></td>
</tr>
<tr>
<td>Mucosal</td>
<td>8</td>
<td>25.7500</td>
<td>12.98075</td>
<td></td>
</tr>
</tbody>
</table>

VIS = vitiligo impact scale.

longer duration of disease (>15 years; 29.91±15.03). Higher scores were observed in divorced patients (29.00±10.81), those with skin type V (28.64±15.61) and who had lesions on exposed parts (25.68±14.66) especially facial (29.52±20.11) and mucosal lesions (28.25±15.53). Scores were lowest in skilled workers (19.07±5.34) as compared to other occupational groups (Table 3).

Figure 3A represents scatter plot depicting correlation of VASI score (12.63±8.06) with VitiQoL score (24.89±13.40) in which both the scores were found to have very strong correlation(r value 0.824 and P value < 0.001). On further analysis of the VitiQoL questionnaire, it was observed that female patients had statistically more significant limited social participation (4.21±1.34) and changes in behavioral...
patterns (4.46±1.22) as compared to males (P value < 0.05). Similarly, the stigma and behavior domains of VitiQol score were statistically significant in the age group of 18-29 years (P value < 0.001) as shown in Table 4.

Figure 3B demonstrates statistically significant weak correlation between VitiQoL and VIDA score with the scores being highest in patients with VIDA score of +4.

Furthermore, Intra class Correlation Coefficient (ICC) was used to evaluate the agreement between VIS-22 and VitiQol scores (Table 5). A value of 0.842 was obtained which was interpreted as good concordance between the two QOL scores, thereby implicating that both the scores were equivalent in terms of evaluation of QOL in vitiligo.

Conclusions

There is dearth of data regarding association of QOL indicators in vitiligo with the disease activity and area scores in patients of skin of color, particularly in the Indian scenario, in spite of the fact that highest incidence of the disease has been established in India [17]. Kim et al. and Kostopoulou et al. in their studies, have highlighted the fact that in vitiligo, subjective severity is more relevant than physician-rated severity in predicting QOL [18,19]. Therefore, through this study, we attempted to reprise the existing high incidence of impact on QOL using valid disease specific questionnaires among patients with variable demographics.

Figure 1. (A) Percentage of patients according to severity grade of impact of VIS-22. (B) Comparison of impact of VIS-22 severity scores in males and females. VIS = vitiligo impact scale.
Figure 2. (A) Scatter plot demonstrating the correlation between VIS-22 and VASI score; association of the parameters is shown by solid line (r value 0.693; P value 0.001). (B) Scatter plot demonstrating positive association and significant correlation of VIS-22 with VIDA score; solid line represents the trend line and dotted lines represent the scatter points (r value 0.366; P value < 0.001). VASI = vitiligo area severity index; VIDA = vitiligo disease activity score; VIS = vitiligo impact scale.

Table 2. Correlation of VASI score with VIS-22 score

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean VASI (12.63±8.06)</td>
<td>0</td>
<td>09.54±5.26</td>
<td>13.18±4.77</td>
<td>25.91±11.84</td>
<td>08.00±2.48</td>
<td>0.001</td>
<td>0.693</td>
</tr>
</tbody>
</table>

VASI = vitiligo area severity index; VIS = vitiligo impact scale.
Table 3. Correlation of VitiQoL score with various demographic variables

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>VitiQoL mean</th>
<th>Standard deviation of VitiQoL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>118</td>
<td>24.3390</td>
<td>12.97942</td>
<td>0.474</td>
</tr>
<tr>
<td>M</td>
<td>77</td>
<td>25.7332</td>
<td>14.15437</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>48</td>
<td>26.6042</td>
<td>14.20330</td>
<td>0.034</td>
</tr>
<tr>
<td>30-39</td>
<td>66</td>
<td>22.3485</td>
<td>9.88004</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>46</td>
<td>23.0652</td>
<td>12.16991</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>35</td>
<td>29.7714</td>
<td>17.97398</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>78</td>
<td>27.1154</td>
<td>15.16317</td>
<td>0.021</td>
</tr>
<tr>
<td>3-6</td>
<td>56</td>
<td>23.3214</td>
<td>10.84956</td>
<td></td>
</tr>
<tr>
<td>7-12</td>
<td>31</td>
<td>18.8387</td>
<td>7.16518</td>
<td></td>
</tr>
<tr>
<td>13-15</td>
<td>18</td>
<td>27.2778</td>
<td>16.73603</td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td>12</td>
<td>29.9167</td>
<td>15.03002</td>
<td></td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>57</td>
<td>26.0000</td>
<td>13.82027</td>
<td>0.463</td>
</tr>
<tr>
<td>Negative</td>
<td>138</td>
<td>24.4420</td>
<td>13.30058</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorce</td>
<td>8</td>
<td>29.0000</td>
<td>10.81005</td>
<td>0.564</td>
</tr>
<tr>
<td>Single</td>
<td>70</td>
<td>25.5000</td>
<td>14.94798</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>117</td>
<td>24.2564</td>
<td>12.65807</td>
<td></td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>35</td>
<td>23.2857</td>
<td>12.15723</td>
<td>0.374</td>
</tr>
<tr>
<td>Labour</td>
<td>78</td>
<td>25.5385</td>
<td>13.89075</td>
<td></td>
</tr>
<tr>
<td>Household worker</td>
<td>36</td>
<td>27.7222</td>
<td>16.52982</td>
<td></td>
</tr>
<tr>
<td>Semiskilled</td>
<td>27</td>
<td>23.4444</td>
<td>8.89829</td>
<td></td>
</tr>
<tr>
<td>Skilled</td>
<td>13</td>
<td>19.0769</td>
<td>5.34574</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>6</td>
<td>28.1667</td>
<td>21.02776</td>
<td></td>
</tr>
<tr>
<td><strong>Skin type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>75</td>
<td>26.1733</td>
<td>15.46782</td>
<td>0.186</td>
</tr>
<tr>
<td>Type IV</td>
<td>103</td>
<td>23.3495</td>
<td>11.20899</td>
<td></td>
</tr>
<tr>
<td>Type V</td>
<td>17</td>
<td>28.6471</td>
<td>15.61626</td>
<td></td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>41</td>
<td>25.6829</td>
<td>14.66874</td>
<td>0.782</td>
</tr>
<tr>
<td>Covered</td>
<td>70</td>
<td>25.3571</td>
<td>14.49541</td>
<td></td>
</tr>
<tr>
<td>Exposed+covered</td>
<td>84</td>
<td>24.1310</td>
<td>11.94140</td>
<td></td>
</tr>
<tr>
<td><strong>Individual sites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>7</td>
<td>27.1429</td>
<td>20.41591</td>
<td>0.283</td>
</tr>
<tr>
<td>Face</td>
<td>17</td>
<td>29.5294</td>
<td>20.11566</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>25</td>
<td>28.4800</td>
<td>14.23060</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>28</td>
<td>21.1071</td>
<td>9.08943</td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td>26</td>
<td>26.4615</td>
<td>11.84308</td>
<td></td>
</tr>
<tr>
<td>UL</td>
<td>47</td>
<td>23.0213</td>
<td>13.18842</td>
<td></td>
</tr>
<tr>
<td>LL</td>
<td>31</td>
<td>24.4516</td>
<td>11.45961</td>
<td></td>
</tr>
<tr>
<td>Genital</td>
<td>6</td>
<td>17.6667</td>
<td>3.61478</td>
<td></td>
</tr>
<tr>
<td>Mucosal</td>
<td>8</td>
<td>28.2500</td>
<td>15.53567</td>
<td></td>
</tr>
</tbody>
</table>

LL = lower limbs; UL = upper limbs; VitiQoL = Vitiligo Quality of Life Index.

Despite earlier research done by Hedayat et al, Borimnejad et al and Hammam et al establishing that females had a substantially greater influence on QOL, our study found comparable results with no significant differences between the genders in overall mean VIS-22 and VitiQoL scores [13,20,21]. This emphasizes the fact that the psychological burden of chronic disorders like vitiligo is alike regardless of gender. This is comparable to the studies done by Aghaei et al in Iran, Patvekar et al and Kota et al in India, who found insignificant variance in QOL impairment between men and women using DLQI scores [22-24]. These variable results might be due to cultural and religious differences between various countries.
Figure 3. (A) Scatter plot demonstrating correlation among VitiQol and VASI scores; association of the parameters is shown by the solid line. (r value-0.824; P value 0.001). (B) Scatter plot demonstrating positive association and significant correlation of VitiQol with VIDA score; solid line represents the trend line and dotted lines represent the scatter points (r value 0.352; P value <0.001). VASI = vitiligo area severity index; VIDA = vitiligo disease activity score; Vitiligo Quality of Life Index.

Nonetheless, gender-wise impact of VIS-22 in the present study reflected maximum proportion of females (48.7%) to have a large impact on their QOL, unlike maximum proportion of males (46.7%) who had moderate impact. Likewise, upon assessment of the individual VitiQol domains, it was established that females had higher affliction in two individual domains, participation limitation (P value 0.03) and behavior (P value 0.012). Questions 4, 6, 9 and 14 contributed maximum to the participation limitation scores and questions 8,12 to behavior scores. Considering that vitiligo generates obvious lesions on the skin, this relatively poor QOL in female patients based on behavior component was logically anticipated as they are socially more pressurized, tend to get coerced behaviorally and strive to disguise their patches with camouflage and/or clothing. Furthermore, they exhibit a greater emotional agitation, and the condition has a significant influence on their self-esteem [13,25,26,27,28]. The higher scores of participation limitation found in the present study are contrary to most of the studies done beforehand [13,25,28]. This discrepancy between genders with
Table 4. Descriptive statistics of various domains of Vitiligo Quality of Life Index score according to gender and age groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Limited social participation</th>
<th>Stigma</th>
<th>Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard deviation</td>
<td>Mean</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>3.80</td>
<td>1.21</td>
<td>4.18</td>
</tr>
<tr>
<td>Females</td>
<td>4.21</td>
<td>1.34</td>
<td>4.56</td>
</tr>
<tr>
<td>P value</td>
<td>0.03</td>
<td>0.09</td>
<td>0.012</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>3.63</td>
<td>1.67</td>
<td>4.92</td>
</tr>
<tr>
<td>30-39</td>
<td>3.41</td>
<td>1.04</td>
<td>4.19</td>
</tr>
<tr>
<td>40-49</td>
<td>3.28</td>
<td>1.22</td>
<td>3.27</td>
</tr>
<tr>
<td>&gt;50</td>
<td>3.10</td>
<td>1.12</td>
<td>2.43</td>
</tr>
<tr>
<td>P value</td>
<td>0.282</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 5. Intra-class Correlation Coefficient for VIS-22 and VitiQoL scores (Statistically Significant at p<0.05; CI- Confidence Interval)

<table>
<thead>
<tr>
<th>Scores</th>
<th>Mean + SD</th>
<th>Intra Class Correlation</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIS 22</td>
<td>27.25+11.19</td>
<td>0.842</td>
<td>0.784-0.884</td>
<td>0.000</td>
</tr>
<tr>
<td>VitiQoL</td>
<td>24.89+13.40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; SD = standard deviation; VIS = vitiligo impact scale; VitiQoL = Vitiligo Quality of Life Index.

regards to participation limitation can be explained by the increased constraints on women in terms of aesthetics, which restrain them to carry out daily and leisure activities as freely as men due to myths pertaining to the disease.

Various other factors that were independent predictors of poor QOL in the present study were early adulthood (18-29 years; statistically significant), prolonged disease duration (>15 years; statistically significant), unskilled profession, single and divorced individuals, skin type V and those having lesions on exposed sites. Among early adulthood patients, the behavior and stigma domains were significantly affected in this study. Most of these results seemed to be consistent with various previous studies done on QOL in vitiligo using various scores wherein the frequently observed indicators of worse QOL were prolonged duration of lesions [18,19], having darker skin type [7,25,30] and lesions on exposed sites apart from other factors such as extensive vitiligo, having psychiatric morbidity and previously treated vitiligo [2,7,14,31]. Poorer QOL in individuals having prolonged disease duration is probably attributable to the chronic nature of disease, relapsing and remitting course, non-compliance to treatment along with the cultural influences pertaining to indigenous practices of medicine and assumptions about incurability of vitiligo.

Both men and women with white patches over skin have been considered inappropriate for marriage since time immemorial, and emergence of patches have been cited as grounds for divorce [29,32]. Five out of eight divorced patients professed to vitiligo being the ground for divorce in this study. It is noteworthy that vitiligo impacts not only the diseased individual but also the QOL of their family members including partners [17]. L Al-Mubarak et al in their study inferred that married people QOL was not as poorly influenced as that of single people, similar to the present study wherein both VIS-22 and VitiQoL scores were higher in single patients as the disease probably instils a fear of rejection and decreased future prospects of marriage [33]. Higher values of both QOL scores in household workers and laborers in this study, as compared to lower scores in patients with skilled occupations, signifies the importance of education in reducing the impact of chronic diseases on the individual psychological impairment.

Both the VIS-22 and VitiQoL scores exhibited a statistically significant association with VIDA score (P value<0.001, r value 0.367 and 0.353 respectively), asserting that higher disease activity corresponds to poorer QOL. The only other study done so far comparing VIDA with QOL scores showed statistically insignificant, weakly positive association between VIDA score and DLQI [34].

Gupta et al grouped the questions of VIS 22 in 10 domains comprising attitude, anxiety, social interaction, occupation and so forth [12]. While assessing these individual domains,
the questions related to social interactions (3, 12, 13) and anxiety (2, 11) were found to be the major contributors to the scores in the present study, specifically among those who had lesions on the exposed sites.

Upon severity assessment of VIS-22, 45.4% patients reflected moderate impact and 33.7% had large impact on their QOL, both comprising of the largest burden (79.1%) of the study group, hence reiterating that vitiligo has considerable affliction on QOL. Likewise, Gupta et al, in a study of cohort of 391 vitiligo patients, noted 49.7% patients had large impact on QOL followed by mild impact in 27.7% patients using VIS 22 scores [16].

Higher mean values of VASI score observed in patients who had moderate to large impact on their QOL (P value 0.001; r value 0.693) according to VIS-22 score, demonstrated that more the disease severity, higher the impact on QOL. Similar results were seen by Hammam at al in study done on QOL using DLQI scores [21].

Statistically significant correlation demonstrated in this study between both VIS-22 and Vitiqol with VASI scores (P value 0.001) infers that QOL seemed to be remarkably dependent on the clinical severity scores. Correlation of Vitiqol score with VASI score was slightly higher (r value 0.824, very strong correlation) than with VIS 22 score (r value 0.693, strong correlation). Studies done antecedently corroborating this relationship between QOL and area severity scores are Hammam et al (DLQI and VASI), Parvekar et al (VASI and VIS-22), Hedyat et al (VASI and Vitiqol) and several others [9, 13, 19, 21, 22, 24, 35, 36, 37, 38]. Contrarily, Kota et al in their study established significant correlation of VASI with DLQI but poor correlation with VIS-22 scores [23].

Since neither of the two QOL scores (VIS-22 and Vitiqol) was determined to be superior to the other (ICC 0.842), each of these scores is viable for utilization in skin of color to measure the impact of vitiligo on QOL.

Since it was a hospital-based study, extrapolation of this data at community level may not be representative of the actual disease burden. Moreover, it was a questionnaire-based study lacking any control group. Furthermore, the study population was representative of a group where cultural beliefs and myths pose a greater psychological burden which may not coincide with global figures. The scoring was performed at one point in time and test-retest measurements could not be performed.

In this study, both disease specific QOL scores were compared and correlated with disease severity assessment tools in Indian patients. Additionally, our study emphasizes the importance for dermatologists to integrate QOL assessments in management of vitiligo, in order to assess the extent of activity limitation and psychological burden.

Our data emphasizes the utility of various vitiligo specific QOL scores along with their various domains and graded impact scales. Preliminary psychological screening may assist in timely engagement with multidisciplinary approaches and mental health experts to mitigate the health burdens for these patients. Future prospective studies should focus on identifying inherent fundamental factors in mental health in order to bridge gaps in psychological support to the patients.

Acknowledgement

We thank Dr. M Ramam and Dr. Vishal Gupta, Department of Dermatology, AIIMS, New Delhi, for granting us permission for using VIS-22.

References


34. Belgau m k a r Vc, Ravindranath D, Nupur NW. Impact of Vitiligo on Quality of Life: A Cross-sectional Pilot Study from Western India. Journal of Skin and Stem Cell. 2020;7. DOI: 10.3812/jssc.107184.


Retrospective Analysis of Onychomycosis Risk Factors Using the 2003-2014 National Inpatient Sample

Vrusha K. Shah¹, Amar D. Desai², Shari R. Lipner³

¹ University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
² Rutgers New Jersey Medical School, Newark, NJ, USA
³ Weill Cornell Medicine, Department of Dermatology, New York, NY, USA

Key words: onychomycosis, comorbidity, dermatophytosis, nail, national


Accepted: October 14, 2023; Published: April 2024

Copyright: ©2024 Shah et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Shari R. Lipner, MD, PhD, Associate Professor of Clinical Dermatology, Weill Cornell Medicine, 1305 York Avenue, 9th Floor, New York, NY 10012. Tel. (646) 962-3376 E-mail: shl9032@med.cornell.edu

ABSTRACT

Introduction: Onychomycosis, a fungal nail infection, is associated with significant morbidity and negative impact on quality of life. Therefore, understanding associated risk factors may inform onychomycosis screening guidelines.

Objectives: This retrospective study investigated common demographic and comorbidity risk factors among hospitalized patients using the National Inpatient Sample.

Methods: The 2003-2014 National Inpatient Sample (NIS) database was used to identify onychomycosis cases and age and sex matched controls in a 1:2 ratio. Chi-square tests and T-tests for independent samples were utilized to compare categorical and continuous patient factors. Demographic and comorbidity variables significant (P < 0.05) on univariate analysis were analyzed via a multivariate regression model with Bonferroni correction (P < 0.0029).

Results: 119,662 onychomycosis cases and 239,324 controls were identified. Compared to controls, onychomycosis patients frequently were White (69.0% versus 68.0%; P < 0.001), Black (17.9% versus 5.8%; P < 0.0001), and insured by Medicare or Medicaid (80.1% versus 71.1%; P < 0.0001). Patients had greater hospital stays (9.69 versus 5.39 days; P < 0.0001) and costs ($39,925 versus $36,720; P < 0.001) compared to controls. On multivariate analysis, onychomycosis was commonly associated with tinea pedis (odds ratio [OR]: 111.993; P < 0.0001), human immunodeficiency virus (OR: 4.372; P < 0.001), venous insufficiency (OR: 6.916; P < 0.0001), and psoriasis (OR: 3.668; P < 0.001).

Conclusions: Onychomycosis patients had longer hospital stays and greater costs compared to controls. Black patients were disproportionately represented among cases compared to controls. Onychomycosis was associated with tinea pedis, venous insufficiency, human immunodeficiency virus, psoriasis, obesity (body mass index [BMI] ≥ 30 kg/m²), peripheral vascular disease, and diabetes with chronic complications, suggesting that inpatients with onychomycosis should be screened for these conditions.
Introduction

Onychomycosis, a fungal nail infection, is the most frequent nail condition seen in the clinical setting worldwide [1-4]. Onychomycosis is not just a cosmetic problem, and patients often have poor quality of life both physically and psychologically. Fortunately, timely and adequate treatment treats diseases and alleviates patient distress [5-7]. Onychomycosis prevalence is more common among men and increases with older age [8-10], and was the most common nail diagnosis among ambulatory care patients in the United States from 2007-2016 [11]. Previous studies have analyzed associations of comorbidity risk factors with onychomycosis and their impact on prognosis [12-18]. A comprehensive analysis of risk factors among a large, matched, and nationally representative cohort of hospitalized onychomycosis patients may help to develop screening guidelines in the United States.

Objectives

The primary objective was to identify risk factors associated with development of onychomycosis among hospitalized patients compared to age and gender matched controls. The secondary objective was to characterize demographics of onychomycosis patients compared to controls.

Methods

The 2003-2014 National Inpatient Sample (NIS) database, a publicly available all-payer inpatient healthcare database developed for the Healthcare Cost and Utilization Project (HCUP) that contains unweighted data for about 7 million hospital stays each year [19], was utilized for this retrospective analysis. NIS was queried using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 110.1 for “Dermatophytosis of nail”, yielding 119,687 cases. Cases were matched to controls in a 1:2 ratio by age and sex. We analyzed demographics (age, sex, race), other patient information (quarter of discharge, length of stay, hospital costs/deaths, hospital region, insurance type), and associated comorbidities.

The most common comorbidities associated with a diagnosis of onychomycosis from available variables in the National Inpatient Sample were identified through a descending counts frequency analysis. Co-morbidities of interest that were unavailable through NIS including tinea pedis, hyperhidrosis, venous insufficiency, and psoriasis were identified through ICD-9-CM codes which were recoded into new variables (Table 1).

Statistical analyses were completed using IBM SPSS software v28.0.1.1. Patient distribution of demographic factors (age, sex, race), other patient information (quarter of discharge, hospital deaths, hospital region, insurance type), and

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICD-9 Codes for Each Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea Pedis</td>
<td>110.4</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>780.8, 705.21, 705.22</td>
</tr>
<tr>
<td>Diabetes with chronic complications</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Diabetes without chronic complications</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Human Immunodeficiency virus/AIDS</td>
<td>042, V08</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>454.0, 454.1, 454.2, 454.8, 454.9, 459.10, 459.11, 459.12, 459.13, 459.19, 459.2, 459.30, 459.31, 459.32, 459.33, 459.39, 459.81, 459.89</td>
</tr>
<tr>
<td>Obesity (body mass index ≥ 30 kg/m2)</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>696.0, 696.1</td>
</tr>
<tr>
<td>Deficiency Anemias</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Chronic Pulmonary Disease</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Depression</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
<tr>
<td>Fluid and Electrolyte Disorders</td>
<td>Co-morbidity variable provided by the National Inpatient Sample database</td>
</tr>
</tbody>
</table>
associated comorbidities were compared between cases and controls using chi-square tests with a 0.05 level of significance. T-tests for independent samples were used to compare distributions of continuous variables including length of stay and hospital costs between cases and controls with a 0.05 level of significance. Demographic factors including age, sex, and race as well as co-morbidity variables were analyzed using univariate logistic regression with a 0.05 level of significance. Variables significant on univariate logistic regression were included in the multivariate regression model, performed with Bonferroni correction (P < 0.0029).

The authors confirm that the ethical policies of the journal have been followed. As this study was IRB exempt due to utilization of publicly available and deidentified data, no ethical approval was needed.

## Results

We identified a total of 119,662 onychomycosis cases and 239,324 controls (Table 2). Age and sex were matched between onychomycosis cases and controls with 56.7% males (P = 1.000) and 63.1% being 65 years or older (P = 1.000). Onychomycosis versus control patients were most frequently White (69.0% versus 68.0%; P < 0.001), followed by Black (17.9% versus 5.8%; P < 0.0001) and Native American (0.5% versus 0.3%; P < 0.001), and were less likely to be Hispanic (9.1% versus 17.4%; P < 0.0001) and Asian or Pacific Islander (1.0% versus 6.7%; P < 0.0001). There was an even distribution of quarter of discharge between cases and controls though onychomycosis cases were slightly more likely to be discharged in the winter months.

### Table 2. Patient Descriptive Factor Distributions among Onychomycosis Patients Compared to Controls (1:2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Onychomycosis Cases (N = 119662)</th>
<th>Matched Controls (N = 239324)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (N, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67807 (56.7%)</td>
<td>135614 (56.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>51855 (43.3%)</td>
<td>103710 (43.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age group (years) N, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-17</td>
<td>427 (0.4%)</td>
<td>854 (0.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>18-64</td>
<td>43713 (36.5%)</td>
<td>87426 (36.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>65+</td>
<td>75522 (63.1%)</td>
<td>151044 (63.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Race (N, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>69285 (69.0%)</td>
<td>157723 (68.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>18001 (17.9%)</td>
<td>13482 (5.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9121 (9.1%)</td>
<td>40385 (17.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>995 (1.0%)</td>
<td>15399 (6.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Native American</td>
<td>465 (0.5%)</td>
<td>645 (0.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>2567 (2.6%)</td>
<td>4226 (1.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Quarter of Discharge (N, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (January-March)</td>
<td>31706 (26.5%)</td>
<td>60321 (25.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 (April - June)</td>
<td>29752 (24.9%)</td>
<td>59652 (24.9%)</td>
<td>0.884</td>
</tr>
<tr>
<td>3 (July-September)</td>
<td>29123 (24.4%)</td>
<td>59021 (24.7%)</td>
<td>0.062</td>
</tr>
<tr>
<td>4 (October-December)</td>
<td>28891 (24.2%)</td>
<td>60330 (25.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hospital data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (days ± standard error (SE))</td>
<td>9.69 ± 0.041</td>
<td>5.39 ± 0.016</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital costs (dollars ± SE)</td>
<td>39925 ± 187,920</td>
<td>36720 ± 119,819</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization deaths (N, %)</td>
<td>1624 (1.4%)</td>
<td>9793 (4.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hospital region N, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>31453 (26.3%)</td>
<td>4606 (1.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Midwest or North Central</td>
<td>39012 (32.6%)</td>
<td>1292 (0.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>South</td>
<td>33116 (27.7%)</td>
<td>8297 (3.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>West</td>
<td>16081 (13.4%)</td>
<td>225129 (94.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Insurance type (N, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Government</td>
<td>95833 (80.1%)</td>
<td>170119 (71.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medicare</td>
<td>83313 (69.6%)</td>
<td>147636 (61.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medicaid</td>
<td>12520 (10.5%)</td>
<td>22483 (9.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Private</td>
<td>17104 (14.3%)</td>
<td>54550 (22.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other type</td>
<td>6552 (5.5%)</td>
<td>14552 (6.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Patient Comorbidity Distribution among Onychomycosis Patients Compared to Controls (1:2)

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Onychomycosis Cases (N = 119662)</th>
<th>Matched Controls (N = 239324)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea Pedis</td>
<td>8204 (6.9%)</td>
<td>167 (0.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>54 (&lt;0.01%)</td>
<td>114 (&lt;0.01%)</td>
<td>0.743</td>
</tr>
<tr>
<td>Diabetes with chronic complications</td>
<td>14942 (12.6%)</td>
<td>11425 (4.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes without chronic complications</td>
<td>26505 (22.3%)</td>
<td>44934 (18.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Human Immunodeficiency virus/AIDS</td>
<td>1457 (1.2%)</td>
<td>715 (0.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>17681 (14.9%)</td>
<td>13894 (5.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>9987 (8.3%)</td>
<td>2362 (1.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obesity (body mass index ≥ 30 kg/m²)</td>
<td>17940 (15.1%)</td>
<td>12448 (5.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1286 (1.1%)</td>
<td>678 (0.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deficiency Anemias</td>
<td>26423 (22.2%)</td>
<td>36525 (15.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72414 (60.8%)</td>
<td>118352 (49.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic Pulmonary Disease</td>
<td>27023 (22.7%)</td>
<td>42336 (17.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>16846 (14.2%)</td>
<td>23461 (9.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Depression</td>
<td>11928 (10.0%)</td>
<td>15476 (6.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>13846 (11.6%)</td>
<td>22312 (9.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>15925 (13.4%)</td>
<td>14130 (5.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fluid and Electrolyte Disorders</td>
<td>30396 (25.5%)</td>
<td>44586 (18.6%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

from January to March (26.5% versus 25.2%; P < 0.001) and less likely to be discharged in the fall season from October to December (24.2% versus 25.2%; P < 0.001). Onychomycosis patients were also more likely to be publicly insured by Medicare (69.9% versus 61.7%; P < 0.0001) and Medicaid (10.5% versus 9.4%; P < 0.01) and less likely to have private insurance (14.3% versus 22.8%; P < 0.0001) than controls. Furthermore, onychomycosis patients versus controls had greater lengths of stay (9.69 versus 5.39 days; P < 0.0001), greater hospital costs (39,925 versus 36,720 dollars; P < 0.0001), but fewer hospitalization deaths (1624 versus 9793 deaths; P < 0.0001). A majority of onychomycosis cases were seen in hospitals in the Northeast (26.3% versus 1.9%; P < 0.0001), Midwest or North Central (32.6% versus 0.5%; P < 0.0001), and Southern United States (27.7% versus 3.5%; P < 0.0001).

A descending counts frequency analysis used to identify the most common comorbidities associated with onychomycosis from variables available in NIS showed that hypertension (60.8%), fluid and electrolyte disorders (25.5%), chronic pulmonary disease (22.7%), diabetes without chronic complications (22.3%), deficiency anemias (22.2%), obesity (defined as a body mass index (BMI) of greater than 30 kg/m²) (15.1%), peripheral vascular disease (14.9%), congestive heart failure (14.2%), renal failure (13.4%), diabetes with chronic complications (12.6%), hypothyroidism (11.6%), depression (10.0%), and venous insufficiency (8.3%) were most represented and were included in the analysis. Using Chi-square analysis, onychomycosis versus control patients more often had all associated comorbidities studied compared to controls (Table 3). The most commonly represented comorbidities in onychomycosis versus control patients included hypertension (60.8% versus 49.5%; P < 0.0001), fluid and electrolyte disorders (25.5% versus 18.6%; P < 0.0001), chronic pulmonary disease (22.7% versus 17.7%; P < 0.001), diabetes without chronic complications (22.3% versus 18.8%; P < 0.001), and deficiency anemias (22.2% versus 15.3%; P < 0.0001).

Using univariate and multivariate logistic regression models, Black (odds ratio [OR]: 2.734; P < 0.0001) and Native American (OR: 1.430; P < 0.001) individuals had greater risk of having onychomycosis than White individuals (Table 4). All comorbidities were significantly associated with greater risk of onychomycosis except hyperhidrosis (OR: 0.947; P = 0.743). The comorbidities most commonly associated with onychomycosis included tinea pedis (OR: 111.993; P < 0.0001), venous insufficiency (OR: 6.916; P < 0.0001), human immunodeficiency virus (OR: 4.372; P < 0.001), psoriasis (OR: 3.668; P < 0.001), obesity (OR: 2.407; P < 0.0001), peripheral vascular disease (OR: 2.294; P < 0.0001), and diabetes with chronic complications (OR: 2.047; P < 0.0001).

Conclusions

In this representative inpatient cohort, we found that onychomycosis was most commonly associated with tinea pedis, human immunodeficiency virus, venous insufficiency, psoriasis, and diabetes mellitus. Given the longer hospital stays and
greater costs among the onychomycosis cohort as compared to controls, understanding associated demographics and co-morbidities may be used to develop onychomycosis screening guidelines among hospitalized patients.

With multivariate analysis, we found that onychomycosis patients were more often Black compared to patients of other races. A 2023 study from the All of Us initiative linking survey and electronic health record data also found that Black individuals (OR: 1.29; 95% confidence interval [CI]: 1.23-1.36) were more likely to develop onychomycosis compared to White individuals [20]. In contrast, this same study found that Hispanic individuals (OR: 1.24; 95% CI: 1.17-1.31) were more likely to develop onychomycosis compared to White individuals. A 2021 systematic review of onychomycosis clinical trials demonstrated that only 32/182 (17.5%) of onychomycosis trials reported race and/or ethnicity, with only 1613/8270 (19.5%) non-white participants represented among studies between 2005-2020 [21]. Since our data, as well as previous research found that Blacks were more likely to have onychomycosis compared to other races, our study highlights the need to include more diverse participants in onychomycosis clinical trials.

We also found that the majority of onychomycosis patients versus controls presented in hospitals in the Northeast, Midwest or North Central, and Southern United States. In contrast, in a study analyzing data from the Porter Novelli summer 2022 ConsumerStyles survey, there was no difference (P = 0.621) in proportions of onychomycosis cases (N = 415) versus controls (N = 3727) by census regions, specifically in the Northeast (18.1% versus 17.2%), Midwest (18.1% versus 21.0%), South (38.1% versus 38.2%), and West (25.8% versus 23.7%) [22]. The difference between...
our 2003-2014 results and the 2022 ConsumerStyles data might suggest that onychomycosis prevalence has changed over time and has now taken on a roughly equal distribution by region or that there are differences between the inpatient and outpatient burdens of onychomycosis.

Furthermore, compared to controls, onychomycosis patients were more likely to be discharged between January and March which is typically winter season. Similarly, a retrospective study of 59 pediatric (age <18 years) onychomycosis patients seen at a dermatology clinic in Donguk University Gyeongju Hospital, Korea found that a majority (N = 22, 37.3%) of patients developed onychomycosis during the winter months (December through February) [23]. Greater discharge frequency during the colder months may be partly attributed to dampness experienced in the winter season along with wearing closed-toed shoes which may increase risk of onychomycosis.

With multivariate analysis, tinea pedis was the most commonly represented comorbidity among onychomycosis patients in our cohort, which is consistent with a 1999-2004 retrospective study analyzing 311 toenail clippings, in which, of thirty-three toenail clippings from patients who also had tinea pedis, 23 showed presence of dermatophytes and ten lacked dermatophytes [24]. Therefore, with concomitant tinea, odds of having versus not having onychomycosis was 2.73 (P < 0.001). Similarly, in a prospective epidemiological study on the prevalence of tinea pedis and concurrent onychomycosis among males residing in two boarding schools in Turkey found that among 410 males, 51.5% (N = 211) of residents had tinea pedis with 14.2% (N = 30) of tinea pedis cases having concurrent toenail onychomycosis [25]. In a 2015 multicenter, double-blinded, 48-week randomized (3:1) controlled trial of 1,655 patients assessing efinaconazole efficacy compared to vehicle for onychomycosis treatment, there was a 29.4% (P = 0.003) versus 16.1% (P = 0.045) cure rate with efinaconazole when treating versus not treating coexisting tinea pedis, respectively [26]. Therefore, early identification of tinea pedis may reduce onychomycosis risk and treatment of coexisting tinea pedis improves outcomes for onychomycosis patients.

We also found a significant correlation between venous and peripheral vascular disease with onychomycosis, consistent with prior studies. In a 2005 cross-sectional study, among 42 outpatient onychomycosis patients and 39 controls, venous insufficiency was more frequent among onychomycosis patients versus controls (15/42, 35.7% versus 6/39, 15.4%; P = 0.037) [27]. Furthermore, in a 2000 prospective epidemiological study of 254 patients presenting to a vascular clinic, there was a significant association between onychomycosis and peripheral arterial disease (ROR: 4.8, P =0.02) [28].

Obesity was relatively common in onychomycosis patients compared to controls with multivariate regression analysis. In a 2002 Hong Kong epidemiological study of 1014 patients with foot diseases, including onychomycosis, risk factors included vascular disease, diabetes, and obesity [29]. Similarly, in a 2009-2010 study of adult patients hospitalized in inpatient clinics at the Haydarpaşa Numune Training and Research Hospital in Turkey, onychomycosis was more prevalent among the obese patients (BMI ≥ 30 kg/m²) as compared to controls (91/250, 36.4% versus 19/120, 15.8%; P < 0.001) [30]. In addition, in a 2004-2005 nested case-control study of 1245 patients with type 2 diabetes mellitus from a Taiwanese clinic, in onychomycosis patients, odds of obesity (BMI ≥ 27 kg/m²) versus normal weight was 2.31 (95% CI: 1.45-3.13; p=0.001) [31]. Therefore, we propose for obese patients to be screened for onychomycosis.

Human immunodeficiency virus (HIV) was also significantly associated with onychomycosis risk in our study, similar to previous literature. In a 2011 study of 100 HIV and acquired immunodeficiency syndrome (AIDS) patients attending Hospital Correia Picanço in Brazil, 32 were diagnosed with onychomycosis [32]. In a 2011 retrospective chart review study of 280 Mexican patients with HIV, 20% (N = 54) had onychomycosis [33]. In another observational cross-sectional study of 205 Mexican patients attending an HIV/AIDS clinic, 26.3% (N = 54) had onychomycosis, and HIV+ patients with versus without onychomycosis had lower CD4+ cell counts at 379.5 cells/μL versus 448 cells/μL respectively (no p-value reported) [34]. Therefore, our study corroborates that HIV infection may be a risk factor for onychomycosis, which may help to inform screening guidelines.

We also found that psoriasis was associated with a greater risk of onychomycosis. The relationship between onychomycosis and psoriasis remains controversial [35,36]. Some studies have found a positive association between onychomycosis and psoriasis. For example, in a 2017-2018 Brazilian cross-sectional outpatient study of 38 patients with psoriasis, 57.9% (N = 22) of patients had onychomycosis [35]. In a 2003-2005 prospective study of 113 psoriatic patients and 106 non-psoriatic controls, 47.6% and 28.4% (P = 0.0054) were diagnosed with toenail onychomycosis respectively [37]. However, other studies have shown a lesser prevalence of onychomycosis among psoriasis patients. For example, a prospective controlled trial of psoriasis patients seen at a dermatology outpatient clinic in Turkey found that, of the 168 psoriasis patients and 164 controls, 13.1% (N = 22) and 7.9% (N = 13) of patients had onychomycosis, respectively (P > 0.05) [38].

Furthermore, in our study, patients with diabetes had increased risk of onychomycosis development similar to previous literature. For example, in a 2016 Italian retrospective
study including 668 non-diabetic and 47 diabetic patients, 55.3% (N = 26) of diabetic patients and 25.2% (N = 169) of non-diabetic patients were diagnosed with onychomycosis (P < 0.0001) [39]. In a 2008-2009 Japanese cross-sectional observational study of 71 patients, an unadjusted multiple logistic regression model found that not washing feet everyday was associated with a significantly increased risk of onychomycosis among diabetic patients (OR: 3.45, 95% CI: 1.24-9.65; P = 0.018), though data was not significant in the age and sex adjusted model (OR: 2.37, 95% CI: 0.76-7.33; P = 0.136) [40]. We found a greater risk of onychomycosis among patients with diabetes with chronic complications compared to those without chronic complications, suggesting that better diabetic control may decrease onychomycosis risk.

We also found significant relationships between onychomycosis and depression, deficiency anemias, and fluid and electrolyte disorders. These comorbidities and their mechanisms leading to onychomycosis development have not been studied extensively, and may be a topic for future research.

Limitations of this study include its retrospective nature and inclusion of only inpatient data. Therefore, these trends, common risk factors, and the overall burden of onychomycosis may not be generalizable to the outpatient setting. In addition, onychomycosis cases were not necessarily mycologically confirmed. Data on diagnosing physician specialty were unavailable. Furthermore, we used International Classification of Diseases, 9th edition codes to create the comorbidity variables for tinea pedis, human immunodeficiency virus, hyperhidrosis, and psoriasis. Consequently, cases with the comorbidity that were not classified within the ICD-9 codes we included may have been missed. There may also have been missing data among the variables we included using the National Inpatient Sample. Further, inaccurate ICD-9 coding of conditions could have affected our data by including cases that were incorrectly classified as onychomycosis in our analysis. Our study was limited to NIS data 2003-2014, and studies analyzing more recent data are warranted.

In sum, in this inpatient cohort, we identified numerous comorbidity risk factors associated with an increased risk of developing onychomycosis among hospitalized patients including tinea pedis, venous insufficiency, human immunodeficiency virus, psoriasis, obesity, peripheral vascular disease, and diabetes with chronic complications. Black patients were disproportionately represented among onychomycosis cases compared to controls. Onychomycosis patients were more likely to have longer hospital stays and greater costs. As onychomycosis has significant impact on quality of life, understanding associated risk factors may help formulate onychomycosis screening guidelines, initiate early treatment/ intervention, and alleviate the burden of onychomycosis in the inpatient setting.

References


The Contact Sensitivity of Turkish Children and Adolescents to European Baseline Series Allergens between 2013 and 2023

Incilay Kalay Yildizhan¹, Ayse Boyvat¹

1 Department of Dermatology, School of Medicine, Ankara University, Ankara, Turkey

Key words: contact sensitivity, children, pediatric, allergens, patch testing, Turkey

Citation: Kalay Yildizhan I, Boyvat A. The Contact Sensitivity of Turkish Children and Adolescents to European Baseline Series Allergens between 2013 and 2023. Dermatol Pract Concept. 2024;14(2):e2024151. DOI: https://doi.org/10.5826/dpc.1402a151

Accepted: November 11, 2023; Published: April 2024

Copyright: ©2024 Kalay Yildizhan et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: Both the authors have contributed significantly to this publication. Incilay Kalay Yildizhan: Conceptualization; methodology; Data curation; investigation; writing-original draft; writing-review and editing. Ayse Boyvat: Project administration; supervision; writing-review and editing.

Corresponding Author: Incilay Kalay Yildizhan, Ankara Universitesi Tip Fakultesi Ibni Sina Hastanesi Yerleskesi 10. Kat B Blok Sihhiye 06100, Ankara, Turkey. Phone: +90 505 6547721 Fax number: +90 312 5082231 E-mail: incilaykalay@gmail.com

Introduction: Increasing the numbers of patch testing in suspected children increases the rate of diagnosis of allergic contact dermatitis and the identification of clinically relevant allergens.

Objective: The aim of this study was to identify the most frequently observed allergens among Turkish children and adolescents patch-tested in 2013–2023.

Methods: The patch test results of 160 patients (age ≤18) were analyzed retrospectively. The frequency of contact allergens and distribution of positive results in terms of sex, age group (children and adolescents), and the presence of atopic dermatitis (AD) were identified.

Results: Forty-nine patients (30.6%) (34 girls and 15 boys) exhibited positive patch test reactions to a minimum of one allergen, and contact sensitivity was statistically significantly higher in girls (P=0.034). The five most frequent allergens were nickel sulfate (10.6%), MCI/MI (8.1%), cobalt chloride (5.6%), p-phenylenediamine (PPD) (5%), and MI (3.5%). No significant association was observed between patch test positivity and age groups (P>.05). Nickel sulfate sensitivity was significantly higher in girls than in boys (P=.043). A positive reaction was detected in 31.3% of patients with AD and in 33.7% of those without (P>.05), and a statistically significant relationship was observed between contact sensitivity to fragrance allergens and AD (P=.046).

Conclusion: Metals and preservatives represent the most frequent allergens in Turkish children and adolescents. Metal sensitivity is expected to decrease as legislation is enforced. Regulatory measures are now required to reduce MI and MCI/MI contact allergy in Turkey.
Introduction

The prevalence of pediatric allergic contact dermatitis (ACD) was previously underestimated because traditional ACD was regarded as very rare in children. This derived from the belief that children have an immature immune system and are less frequently exposed to contact allergens [1]. However, recent studies have confirmed an increase in positive patch test results in children [2]. The meta-analysis by Bonitsis et al. [3] reported a higher proportion of positive reactions in studies published after 1995 [4]. The rate of positive patch test reactions in the pediatric age group ranges from 27% to 95.6% in recent studies, while relevance ranges from 30.5% to 92.6% [5]. Variations in the prevalence of contact sensitivity to allergens are observed between countries due to differences in allergen exposures, legislations, and local cultures. In previous studies from Turkey, the patch test positivity rate in children ranged between 32% and 57.5% [6-10].

Objective

Limited data are available for patch test results among Turkish children. The aim of this study was to determine the prevalence of ACD and the most common allergens in children and adolescents attending our referral patch testing center in Turkey.

Materials and Method

Approval was granted by the Ankara University Faculty of Medicine ethical committee (n. 02-133-19). One hundred and sixty children and adolescents with clinically suspected ACD who underwent patch testing based on the European Baseline Series (EBS, Chemotechnique Diagnostics, Vellinge, Sweden) at the Ankara University School of Medicine Dermatology Department in 2013–2023 were enrolled. Demographic characteristics, personal and family histories of atopy, duration, and localization of lesions, and patch test findings were retrieved retrospectively from chart reviews. Localizations were classified as the hands, face/head/neck, leg, trunk, or generalized. Allergen groups were classified as metals, fragrances, preservatives, rubber additives, and topical treatments. The patients were divided into two age categories: children (≤10 years) and adolescents (11–18 years).

The allergens were applied to the upper back using Van der Bend chambers. These were removed on Day 2, and reading was conducted after 30 minutes. A final reading and evaluation were conducted on Day 4. The results were assessed based on the scoring system recommended by the International Contact Dermatitis Research Group (ICDRG) [11]. Reactions of 1+ or more were regarded as positive. Irritant, doubtful, and negative responses were recorded as negative.

The EBS underwent several modifications during the study period. Test results based on the EBS applicable during the study period were included in the analysis. SPSS software (SPSS for Windows, Version 15.0, SPSS Inc., USA) was used for statistical analyses. Qualitative variables are expressed as number and percentage values at a 95% confidence interval, while quantitative variables are expressed as mean ± standard deviation (SD). Categorical variables were compared using the chi-square and Fisher’s exact tests, while the Mann-Whitney U and Student’s t tests were applied to compare parametric values. P values <0.05 were considered statistically significant.

Results

One hundred and sixty children and adolescents aged 2–18 were patch-tested during the study period. The study group consisted of 91 girls (56.9%) and 69 boys (43.1%), with a mean age of 12.4± 4.1 years (median 13 years, range 2–18 years). Sixty-eight (42.5%) patients reported a history of atopy, with a family history of atopy being reported in 31 (19.4%) patients, and personal atopy in 51 (31.9%). Atopic dermatitis (AD) based on the Hanifin and Rajka criteria was present in 36 (22.5%) patients [12]. The median duration of symptoms was 12 months (mean 22.6±23.9, range 1–120 months). The most common primary site of dermatitis was the hands (n=77, 48.1%), followed by the face/head/neck (n=35, 21.9%), the leg/foot (n=18, 11.4%), and generalized lesions (n=18, 17.4%).

Forty-nine patients (30.6%) (34 girls and 15 boys) exhibited positive patch test reactions to a minimum of one allergen (range 1–7). Thirty-one patients (19.4%) were positive to one allergen, 13 (8.1%) to two, three (1.9%) to three, one (0.8%) to four, and one (0.8%) to seven. Overall, there were 77 positive reactions to EBS allergens. The distribution of frequencies of contact sensitization to EBS allergens is presented in Table 1. The five most common allergens were nickel sulfate (n=17, 10.6%), MCI/MI (n=13, 8.1%), cobalt chloride (n=9, 5.6%), p-phenylenediamine (PPD) (n=8, 5%), and MI (n=4, 3.5%). Metal allergens were the most common group (n=22, 13.8%), followed by preservatives (n=16, 10%), dyes (n=10, 6.2%), and fragrances (n=7, 4.4%). A significantly higher prevalence of contact sensitivity to cobalt chloride was observed among patients with positive responses to nickel sulfate (P=.008). Four patients with positive reaction to MI and three with positive reaction to MDBG exhibited concomitant sensitivity to MCI/MI (P<.001).

The frequencies of contact sensitization to EBS allergens and distributions of positivity according to sex, atopic dermatitis, and age groups are given in Table 1. Prevalences of contact sensitivity were 21.7% in boys and 37.4% in girls. Contact sensitivity was statistically significantly higher
**Table 1:** Frequency of contact sensitization to EBS allergens and distributions of positivity according to sex, atopic dermatitis, and age group.

<table>
<thead>
<tr>
<th>Allergen Description</th>
<th>Number of Positive Reactions/Total Number of Tested Patients</th>
<th>Prevalence % (95% CI)</th>
<th>Sex N(%)</th>
<th>P value</th>
<th>Atopic Dermatitis N(%)</th>
<th>P value</th>
<th>Age Group N(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AD</td>
<td>Non-AD</td>
<td>Children</td>
<td>Adolescent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Boy</strong></td>
<td><strong>Girl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium dichromate 0.5% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Phenylenediamine 1.0% pet</td>
<td>8/160</td>
<td>5.8%</td>
<td>3 (4.3)</td>
<td>5 (5.5)</td>
<td>&gt;.99</td>
<td>1 (2.8)</td>
<td>7 (5.6)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Thiuram mix 1.0% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>-</td>
<td>1 (1.1)</td>
<td>-</td>
<td>-</td>
<td>1 (0.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Neomycin sulfate 20.0% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt chloride 1.0% pet</td>
<td>9/160</td>
<td>5.6%</td>
<td>4 (5.8)</td>
<td>5 (5.5)</td>
<td>&gt;.99</td>
<td>1 (2.8)</td>
<td>8 (6.5)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Benzocaine 10.0% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel sulfate 5.0% pet</td>
<td>17/160</td>
<td>10.6%</td>
<td>2 (2.9)</td>
<td>15 (16.5)</td>
<td>.008</td>
<td>5 (13.9)</td>
<td>12 (9.7)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Clioquinol 5.0% pet</td>
<td>0/93</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colophony 20.0% pet</td>
<td>3/160</td>
<td>1.9%</td>
<td>1 (1.4)</td>
<td>2 (2.2)</td>
<td>&gt;.99</td>
<td>0 (2.4)</td>
<td>&gt;.99</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Paraben mix 16.0% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>0</td>
<td>1 (1.1)</td>
<td>-</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>N-Isopropyl-N-phenyl-4-phenylenediamine 0.1% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>1 (1.4)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Lanolin Alcohol 30.0% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercapto mix 2.0% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoxy resin 1.0% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>0</td>
<td>1 (1.1)</td>
<td>-</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Myroxylon pereirae resin 25.0% pet</td>
<td>3/160</td>
<td>1.9%</td>
<td>1 (1.4)</td>
<td>2 (2.2)</td>
<td>&gt;.99</td>
<td>3 (8.8)</td>
<td>0</td>
<td>.011</td>
</tr>
<tr>
<td>4-Tert-Butylphenol formaldehyde resin 1.0% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>0</td>
<td>1 (1.1)</td>
<td>-</td>
<td>1 (2.8)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2-Mercaptobenzothiazole (MBT) 2.0% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Formaldehyde 2.0% aq                  | 2/160                                                       | 1.3%                  | 0        | 2 (2.2) | .506 | 0      | 2 (1.6) | >.99 | 0 | 2 (1.9) | >.99
Table 1. Frequency of contact sensitization to EBS allergens and distributions of positivity according to sex, atopic dermatitis, and age group. (continued)

<table>
<thead>
<tr>
<th>EBS allergens</th>
<th>Number of positive reactions/total number of tested patients</th>
<th>Prevalence % (95% CI)</th>
<th>Sex N(%)</th>
<th>P value</th>
<th>Atopic Dermatitis N(%)</th>
<th>P value</th>
<th>Age Group N(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragrance mix I 8.0% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>Boy</td>
<td>0</td>
<td>1 (1.1)</td>
<td>-</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Sesquiterpene Lactone mix 0.1% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quaternum 15 1.0% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>Boy</td>
<td>0</td>
<td>1 (1.1)</td>
<td>-</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Primin 0.01% pet</td>
<td>0/93</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) 0.02% aq</td>
<td>13/160</td>
<td>10.7%</td>
<td>Boy</td>
<td>3 (4.3)</td>
<td>10 (11)</td>
<td>.153</td>
<td>4 (11.1)</td>
<td>9 (7.3)</td>
</tr>
<tr>
<td>Budesonide 0.01% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tixocortol-21-pivalate 0.1% pet</td>
<td>1/160</td>
<td>0.6%</td>
<td>Boy</td>
<td>1 (1.4)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Methylidibromo glutaronitrile 0.5% pet</td>
<td>3/160</td>
<td>1.9%</td>
<td>Boy</td>
<td>0</td>
<td>3 (3.3)</td>
<td>.260</td>
<td>0</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Fragrance mix II 14.0% pet</td>
<td>3/160</td>
<td>1.9%</td>
<td>Boy</td>
<td>1 (1.4)</td>
<td>2 (2.2)</td>
<td>&gt;.99</td>
<td>0</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5.0% pet</td>
<td>0/160</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methylisothiazolinone 0.2% aq</td>
<td>4/113</td>
<td>3.5%</td>
<td>Boy</td>
<td>1 (2.2)</td>
<td>3 (4.5)</td>
<td>.645</td>
<td>1</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Textile dye mix 6.6% pet</td>
<td>2/91</td>
<td>2.1%</td>
<td>Boy</td>
<td>1 (6.3)</td>
<td>1 (2.8)</td>
<td>.525</td>
<td>1</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>2-Hydroxyethyl methacrylate 2.0% pet</td>
<td>0/67</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Propolis 10.0% pet</td>
<td>0/67</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CI: Confidence interval Significant results (P< 0.05) are shown in bold.
in girls (P=0.034). The prevalence of contact allergy to nickel sulfate was significantly higher in girls than in boys (2.9% vs 16.5%) (P=0.008). However, there was no significant association between positive reactions to other allergens and sex (P>.05).

The mean age of the patients with contact sensitivity to EBS allergens was 12.7±4.2 years. No significant association was found between age and patch test positivity (P=.496). Contact sensitivity to at least one allergen was observed in 28.3% (n=15) of the children and 31.8% (n=34) of the adolescents, although the difference was not statistically significant (P=.654). There was also no significant association between the distribution of contact sensitivity rates to each EBS allergen and age groups (P>.05).

Positive reactions to at least one allergen were determined in 29.4% (n=15) of individuals with a personal history of atopy and in 33.3% (n=12) of those diagnosed with AD. No significant difference in positive patch test rates was observed between patients with and without atopy (P>.05). The presence of AD also exhibited no significant effect on contact sensitivity rates (P>.05). However, contact sensitivity to Myroxylon pereirae resin was significantly higher in patients with atopy (P=0.031) and AD (P=.011), and a significant relationship was observed between contact sensitivity to fragrance allergens and individuals with AD (P=.046).

Conclusions

The frequency of positive reactions to EBS allergens in Turkish children and adolescents in this study was 30.6%. Five studies from Turkey reported patch test positivity in 32% to 57.5% of children [6-10]. Zafrir et al. reviewed 50 series from 48 studies from Europe, North America, South America, and Asia. Patch test reaction positivity in children ranged from 14.5% to 70.7% in Europe, 61% to 95.6% in North America, and 45.4% to 80% in Asia [13]. Our result is consistent with some European studies involving EBS allergens, but substantially lower than in the North American studies, which report high sensitization rates. In contrast to contact sensitivity rates, the most common allergens do not differ significantly. Zafrir et al. reported nickel sulfate as the most common allergen, followed by cobalt nitrate, thimerosal, fragrance mix, and potassium dichromate in 48 different international studies [13]. The five most common allergens in the present study were nickel sulfate (n=17, 10.6%), MCI/MI (n=13, 8.1%), cobalt chloride (n=9, 5.6%), p-phenylenediamine (PPD) (n=8, 5%), and MI (n=4, 3.5%).

The prevalence of pediatric nickel-induced ACD in previous studies ranged between 6.8% and 80.4% [13]. The prevalence of contact sensitization to nickel sulfate among Turkish children varied between 7.2% and 46%, and nickel sulfate is also the most common allergen in studies from Turkey [7-10]. The frequency of nickel sensitivity in the pediatric population rises with age, the risk being significantly greater among girls [14]. Nickel allergy prevalences of 13% in girls with pierced ears compared to 1% in those without were reported in one study [15]. The prevalence of contact allergy to nickel sulfate in the present study was also significantly higher among girls (P=.008). Ear piercing in the first 2–3 years of life is a common tradition in Turkey, the holes being kept open by imitation or gold jewelry that may also contain nickel [7]. Turkish legislation limits nickel release to 0.5 µg/cm²/week in items intended for direct contact with the skin [16]. The regulation was fully enforced by the end of 2021, and positive effects on metal sensitivity are anticipated.

Cobalt chloride was another common metal allergen with a 5.6% sensitivity rate and significantly higher in our patients with a positive response to nickel sulfate (P=.008). Positive patch test reactions to cobalt chloride in the pediatric age group ranged between 4.4% and 11.1% [13]. Concomitant nickel and cobalt sensitization may be a result of cross-sensitivity due to the similar atomic structures, or dual sensitization may result after separate or coupled exposure to nickel and cobalt [17].

Preservatives constituted two of the five principal allergens in this study (MCI/MI 8.1%, and MI 3.5%). MCI/MI and MI are isothiazolinone preservatives frequently employed as skin care agents for babies and children as well in cosmetics, household products or water-based paints, glues, and slime. MCI/MI sensitivity rates in children in previous studies ranged from 2.4% in asymptomatic infants to 11.7% in children referred for patch testing [18,19]. Zafrir et al.’s review of 48 studies reported that MCI/MI was not among the five most common allergens in children; however, it has been identified as one of the most common allergens in Turkish children, with 12%–20% sensitivity rates [6,8,10]. Yilmaz et al. reported a low sensitivity rate of MCI/MI (1.9%), but also stressed that the number of patients with MCI/MI-induced ACD rose five-fold in 1996-2006 compared to 2007-2017 [9]. The sensitivity rate of MI in the present study was 3.5%. Turkish cosmetic regulations permit MCI/MI to be used in rinse-off products at a maximum concentration of 15 ppm, while MI can be employed at up to 100 ppm [20]. The presence of MCI/MI and MI in leave-on products in Turkey until 2015 and 2017, respectively, may have caused the high sensitivity rates in our study. Sensitivity to MCI/MI and MI is a major public health problem in Turkey, and regulations are needed to reduce the permitted level of MI in rinse-off cosmetics.

PPD is a significant component of chemical hair dyes and black henna tattoos. In the present study, the contact sensitivity of PPD was 5%, and ranged from 7.1% to 9.5% in other studies from Turkey. These results are slightly higher.
than in other studies from the literature, which reported 3.5% and 4.2% contact sensitivity rates to PPD [21]. Temporary tattoos containing high concentrations of PPD constitute a major cause of sensitivity in Turkish children and adolescents.

The question of whether children with AD are particularly prone to allergic contact dermatitis (ACD) is controversial. A systematic review and meta-analysis reported similar prevalences of contact sensitization in individuals with and without AD, recommending that clinicians should consider patch testing on suspicion of ACD [22]. In a review of 21 studies comparing the patch test results of children with and without AD, the prevalence of contact allergy was significantly higher among children without AD (overall, 41.7% vs 46.6%) [23]. Patch testing may be useful as a screening tool in the management of pediatric AD. It should always be considered in recalcitrant AD or if ACD is indicated by a previous medical history [23]. The allergens to which children with AD react differ significantly from those in children without AD. All children with AD are inevitably chronically exposed to topical agents, and epidermal barrier defects in AD may facilitate sensitization to medications and fragrances. In this study, the contact sensitivity rate to Myroxylon pereirae resin was significantly higher in patients with AD (P=0.011), and a significant relationship was found between the fragrance allergens group and patients with AD (P=.046). A study of 1012 Dutch children reported that individuals with AD reacted significantly more frequently to fragrances (fragrance mix I and Myroxylon pereirae resin) [24]. Personal care products containing fragrances should also be considered as potential causes of ACD in children, especially those with AD. A recent study found that 89% of 187 surveyed products labeled as “hypoallergenic,” “dermatologist recommended/tested,” “fragrance-free,” or “paraben-free” contained at least one contact allergen [25].

In conclusion, metals and preservatives are the main allergens in Turkish children. Legislation that was enacted in 2022 would lower the high nickel sensitivity rates. However, regulations are required to reduce the permitted level of MI in rinse-off cosmetics. The principal limitation of this study is that the clinical relevance of allergens was not investigated.

References
20. Turkish Medicines and Medical Devices Agency: Regulatory and Supervisory Authority. Guidelines for the use of preservatives


A Real-Life 208 Week Single-Centred, Register-Based Retrospective Study Assessing Secukinumab Survival and Long-Term Efficacy and Safety Among Greek Patients with Moderate to Severe Plaque Psoriasis, Including Difficult-to-Treat Manifestations Such as Genitals and Scalp

Eirini Kyrmanidou¹, Christina Kemanetzí¹, Chatzopoulos Stavros², Myrto-Georgia Trakatelli¹, Aikaterini Patsatsi¹, Xenia Madia³, Dimitra Ignatiadi³, Evangelia Kalloniati¹, Zoe Apalla¹, Elizabeth Lazaridou¹

¹ Second Department of Dermatology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece
² School of Statistics and Insurance Science, University of Western Macedonia, Kozani, Greece
³ Novartis, Athens, Greece

Key words: psoriasis, genital psoriasis, scalp psoriasis, secukinumab, Greece


Accepted: December 14, 2023; Published: April 2024

Copyright: ©2024 Kyrmanidou et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: Received a research fund from Novartis, Greece.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Kyrmanidou Eirini, I.Passalidi 77, 55132 Thessaloniki. Email: ekyrmanidou@gmail.com

ABSTRACT

Introduction: Psoriasis is a chronic inflammatory disease with multiple skin manifestations, and in case of lesions affecting the genital area, sexual health impairment and psychological distress can furthermore impair the patients quality of life. Secukinumab is a fully humanized immunoglobulin G1 kappa antagonist of IL-17A and is indicated for the treatment of moderate-to-severe psoriasis, since it shows a significant efficacy in clinical outcomes, with rapid onset of remission, prolonged treatment response rate, advantageous safety profile and a valuable improvement of the patients quality of life.

Objectives: This study was conducted in order to gather retrospective real-world data regarding the efficacy of secukinumab in treating patients with moderate-to-severe plaque psoriasis in Greece. To
Introduction

Psoriasis is a chronic inflammatory disease with multiple skin manifestations and from epidemiological studies in the United States it is estimated that 3% of adult population shows signs of psoriatic disease [1]. 90% of patients with psoriasis have chronic plaque psoriasis, whereas less common psoriasis can affect the nails (23%-27%), face (49%) palms and soles (12%-16%), or intertriginous folds (21%-30%). Quality of life is impaired in patients with psoriasis, especially when sites of aesthetic significance are affected like the scalp and palms [2]. Moreover psoriasis affecting the genital area can lead to sexual health impairment and psychological distress, despite the fact that it only affects ≤ 1% of the body surface area (BSA) [3].

Although the exact pathogenetic mechanism of psoriasis has been under investigation until now, it seems that both genetic and environmental factors lead to an immune mediated hyperproliferation of the epidermal keratinocytes, an aberrant inflammatory infiltration of the dermis and an increased angiogenesis in the psoriatic lesions. Recently, the interleukin-23/T helper 17 (IL-23/Th17) pathway has been recognized as a key axis in the pathogenesis of psoriasis, which leads to the overexpression of the proinflammatory cytokine interleukin 17A (IL-17A). Secukinumab is a fully humanized immunoglobulin G1 kappa antagonist of IL-17A and is indicated for the treatment of moderate-to-severe psoriasis, moderate-to-severe paediatric plaque psoriasis, psoriatic arthritis (PsA), axial spondyloarthritis, juvenile idiopathic arthritis (enthesitis-related arthritis and juvenile psoriatic arthritis) and hidradenitis suppurativa [1-9]. Namely for the treatment of moderate-to-severe plaque psoriasis in adults, secukinumab is indicated as first line treatment. Secukinumab shows a significant efficacy in clinical outcomes, with rapid onset of remission, prolonged treatment response rate, advantageous safety profile and a valuable improvement of patients quality of life, not only from phase-III clinical trials but from real-life data as well [4,5].

Objectives

This study was conducted in order to gather retrospective real-world data regarding the efficacy of secukinumab in treating patients with moderate-to-severe plaque psoriasis at the psoriasis clinic of the Second Dermatology Department of the Aristotle University of Thessaloniki, “Papageorgiou” General Hospital.
Methods

In order to fill the relevant literature gap, we included difficult-to-treat manifestations in our analysis, specifically regarding the efficacy in the genital area and on the skin folds where relevant data are missing both from the drug clinical program as well as from the real-world setting. Frequency of follow-up visits was determined by attending physicians according to routine medical practice, however data were collected at 4, 16, 52, 104 and 208 weeks with a time window (± 1 week) after secukinumab treatment initiation.

Study Design

The Psoriasis Outpatient Clinic Registry of our clinic was reviewed and all adult patients receiving 300 mg secukinumab and attending follow-up visits on a regular basis, according to routine medical practice, were included. The timeline of the study was from 2015 to 2020. Written informed consent was obtained from each patient. Patients, aged ≥18 years, with a clinical diagnosis of chronic (≥ 6 months) moderate-to-severe plaque psoriasis, and candidates for systemic therapy who were receiving secukinumab (as per local label indication and according to routine medical practice) for at least for 16 weeks were included. Patients with a baseline Psoriasis Area and Severity Index (PASI) <10 were also included if the baseline Dermatology Life Quality Index (DLQI) was ≥10 or if there were symptoms in the scalp, genitals, palms, and feet or if onycholysis of at least 3 fingernails was characterized as persistent manifestation according to local and global guidelines. Use of concomitant anti-psoriatic agents (systemic or topical) was permitted as per everyday clinical practice.

Patients were excluded if the medical file data of interest was incomplete for eligibility evaluation and if there were any contradictions to IL-17/secukinumab intake as per label.

Primary endpoint of the study was the percentage of patients who achieved a PASI75 response rate at week 16 and week 52 post baseline. Secondary endpoints were the evaluation at baseline (week 0), week 4 (±1), week 16 (±1), week 52 (±1), and week 104 (±1), week 156 (±1), week 208 (±1) of:

- a. absolute PASI; percentage of patients who achieved PASI75, PASI90, PASI100 response rates,
- b. percentage of patients achieving scalp PGA 0/1 (sPGA)
- c. percentage of patients achieving full/almost full genitals clearing;
- d. percentage of patients achieving full/almost full folds clearing;
- e. incidence of adverse events (AE) and serious adverse events (SAEs) and identification of AE leading to drug discontinuation;
- f. potential predictive clinical variables influencing response at week 52, and 104.

Assessments were collected only when available in routine clinical practice, and they were not prerequisites for study participation.

Statistical Analysis

Frequencies and percentages are given for qualitative variables, while means and standard deviations, as well as medians and interquartile ranges, are given for quantitative variables. Since there were limited cases of loss to follow-up (≤5% of the study sample), effectiveness data were analyzed using an ‘as observed analysis’. Descriptive statistics were performed using relevant Descriptive statistics tests (for example Shapiro–Wilk/Shapiro–Francia test). For the comparison of categorical variables, Chi-Squared and Fisher Exact tests were used, while, depending on the distribution of continuous variables, unpaired t-test and Mann–Whitney U-test were applied. The Chi-Square test was applied to analyze differences in PASI Scores between subgroups of patients, such as PsA and bio-naive patients. Univariable logistic regression analysis considering all variables collected was also performed in order to identify potential links and clinical factors of interest associated with the efficacy as per other similar RWE studies. Multivariable analysis could not be performed due to the high number of independent variables, along with the sample size of present study. All statistical analyses were done with IBM SPSS 27.0 (IBM). Alpha level of significance was set at 0.05.

Results

Ninety-nine patients were included in the study population and their demographic and baseline characteristics are summarized in Table 1. More precisely, 74 (74.75%) patients had scalp involvement, genitals and skin folds were affected in 27 (27.27%) and 17 (17.17%) respectively, and 32 (32.32%) of the studied population had psoriatic arthritis. Sixty-six patients (66.67%) were bio-naive, whereas 33 patients had never received systemic treatment. In the bio-experienced group, 12 patients had received one biologic agent, 12 patients had received two biologic agents and 5 patients had experienced treatment failure of any reason in 3 or more biologic agents. Moreover out of all the studied population 17.17% (17/99), 11.11% (11/99), 12 (12/99), 10.10% (10/99), 2.02% (2/99) had received adalimumab, etanercept, infliximab, ustekinumab and golimumab respectively. PDE4 inhibitors had been prescribed in 14.14% (14/99) of them. Mean BMI index in our study population was 29.3.

Regarding comorbidities 15 patients (15.15%) were obese (BMI>30), 42 patients (42.42%) had Hashimoto disease, 19 patients (19.19%) were diagnosed with depression or anxiety disorder and 8 patients (8.08%) had diabetes mellitus. Overall 53 patients (53.54%) had no comorbidities,
efficacy of secukinumab at week 16, PASI75 was achieved by 84/96 (87.5%) patients, PASI90 by 67/96 (69.8%) and PASI100 by 47/96 (49%) (Table 2). By week 52 PASI75/PASI90/PASI100 was achieved by 86.4%/77.8%/43.2%, by week 104 PASI75/PASI90/PASI100 was achieved by 94.5%/78.2%/47.3% and in 9 patients having completed 208 weeks of therapy PASI100/PASI90 was achieved in a percentage of 88.9%/100% respectively (Table 2).

Aiming to identify potential predictive factors influencing response, univariable analyses were performed at weeks 52 and 104 taking into consideration various parameters, namely age, height, weight, BMI, BSA, disease/therapy duration, previous treatments (conventional/biologic), special manifestations of psoriasis (scalp, nails, genitals, folds) and comorbidities (PsA, obesity, coronary disease, depression).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr, median, range)</td>
<td>99</td>
<td>50 (23-76)</td>
<td></td>
</tr>
<tr>
<td>Sex male</td>
<td>99</td>
<td>53</td>
<td>53.5</td>
</tr>
<tr>
<td>Weight (kg, mean [SD])</td>
<td>99</td>
<td>87.78 [17.98]</td>
<td></td>
</tr>
<tr>
<td>BMI (mean, [SD])</td>
<td>99</td>
<td>29.3 [4.88]</td>
<td></td>
</tr>
<tr>
<td>BSA (mean [SD])</td>
<td>99</td>
<td>27.14 [12.01]</td>
<td></td>
</tr>
<tr>
<td>PASI baseline (mean [SD])</td>
<td>99</td>
<td>12.7 [3.94]</td>
<td></td>
</tr>
<tr>
<td>DLQI baseline (mean [SD])</td>
<td>99</td>
<td>11.68 [2.95]</td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis (N, %)</td>
<td>99</td>
<td>32</td>
<td>32.32</td>
</tr>
<tr>
<td>Previous systemic treatment</td>
<td>99</td>
<td>66</td>
<td>66.67</td>
</tr>
<tr>
<td>Conventional treatment</td>
<td>61/99</td>
<td>61</td>
<td>61.61</td>
</tr>
<tr>
<td>Previous Biological therapy</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologic naive</td>
<td>99</td>
<td>66</td>
<td>66.67</td>
</tr>
<tr>
<td>Psoriasis genital involvement</td>
<td>99</td>
<td>27</td>
<td>27.27</td>
</tr>
<tr>
<td>Psoriasis scalp</td>
<td>99</td>
<td>74</td>
<td>74.74</td>
</tr>
<tr>
<td>Psoriasis involving folds</td>
<td>99</td>
<td>17</td>
<td>17.17</td>
</tr>
<tr>
<td>Psoriasis nails</td>
<td>99</td>
<td>49</td>
<td>49.49</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>N</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Hashimoto disease</td>
<td>99</td>
<td>42</td>
<td>42.42</td>
</tr>
<tr>
<td>Obesity (BMI&gt;30)</td>
<td>99</td>
<td>15</td>
<td>15.15</td>
</tr>
<tr>
<td>Depression</td>
<td>99</td>
<td>12</td>
<td>12.12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>99</td>
<td>8</td>
<td>8.08</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>99</td>
<td>7</td>
<td>7.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>99</td>
<td>6</td>
<td>6.06</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>99</td>
<td>3</td>
<td>3.03</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>99</td>
<td>3</td>
<td>3.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>99</td>
<td>17</td>
<td>17.17</td>
</tr>
<tr>
<td>Patients comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>99</td>
<td>53</td>
<td>53.53</td>
</tr>
<tr>
<td>1-2</td>
<td>99</td>
<td>35</td>
<td>35.05</td>
</tr>
<tr>
<td>&gt;3</td>
<td>99</td>
<td>11</td>
<td>11.11</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index; BSA = Body Surface Area; DLQI = Dermatology Quality of Life Index; SD = standard deviation.

5 patients (5.05%) had one comorbidity, 30 patients (30.30%) had two comorbidities and 11 (11.11%) patients had 3 or more comorbidities. 17.17% of the patients were active smokers (> 10 cigarettes/day).

All patients started receiving secukinumab as monotherapy together with topical steroids and vitamin D analogues. Topical treatment was discontinued by almost all patients (92/99, 93%) by the first follow up visit at week 4. Cyclosporine was added as additional therapy for two patients, for 12 weeks (week 4-week 16) and for 24 weeks (week 60-week 84) respectively. Four patients received methotrexate additionally, two at week 8, one at week 84 and one at week 116 respectively.

Baseline mean PASI, BSA, sPGA and DLQI scores are 12.7, 27.14, 2.2 and 11.68 respectively. Addressing the efficacy of secukinumab at week 16, PASI75 was achieved by 84/96 (87.5%) patients, PASI90 by 67/96 (69.8%) and PASI100 by 47/96 (49%) (Table 2). By week 52 PASI75/PASI90/PASI100 was achieved by 86.4%/77.8%/43.2%, by week 104 PASI75/PASI90/PASI100 was achieved by 94.5%/78.2%/47.3% and in 9 patients having completed 208 weeks of therapy PASI100/PASI90 was achieved in a percentage of 88.9%/100% respectively (Table 2).

Aiming to identify potential predictive factors influencing response, univariable analyses were performed at weeks 52 and 104 taking into consideration various parameters, namely age, height, weight, BMI, BSA, disease/therapy duration, previous treatments (conventional/biologic), special manifestations of psoriasis (scalp, nails, genitals, folds) and comorbidities (PsA, obesity, coronary disease, depression,
Table 2. Clinical efficacy of secukinumab.

<table>
<thead>
<tr>
<th>PASI outcomes</th>
<th>WEEK</th>
<th>N</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>99</td>
<td>55/99  (55.6%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>96</td>
<td>84/96 (87.5%)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>81</td>
<td>70/81 (86.4%)</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>55</td>
<td>52/55 (94.5%)</td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>30</td>
<td>29/30 (96.7%)</td>
</tr>
<tr>
<td></td>
<td>208</td>
<td>9</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>PASI 75</td>
<td>4</td>
<td>99</td>
<td>25/99 (25.3%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>96</td>
<td>67/96 (69.8%)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>81</td>
<td>70/81 (77.8%)</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>55</td>
<td>43/55 (78.2%)</td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>30</td>
<td>24/30 (80.0%)</td>
</tr>
<tr>
<td></td>
<td>208</td>
<td>9</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>PASI 90</td>
<td>4</td>
<td>99</td>
<td>14/99 (14.1%)</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>96</td>
<td>47/96 (49.0%)</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>81</td>
<td>35/81 (43.2%)</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>55</td>
<td>26/55 (47.3%)</td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>30</td>
<td>15/30 (50.0%)</td>
</tr>
<tr>
<td></td>
<td>208</td>
<td>9</td>
<td>8/9 (88.9%)</td>
</tr>
<tr>
<td>PASI 100</td>
<td>4</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>156</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>208</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

PASI = Psoriasis Area and Severity Index.

diabetes mellitus, dyslipidemia, hypertension, Hashimoto disease, anxiety disorder, smoking). In a univariate analysis, no medical, sociodemographic and the assessed clinical biomarker was significantly associated with PASI responses.

Regarding difficult-to-treat manifestations, we recorded scalp involvement in 74.74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (psoriasis inversa) in 17% (17/99). After secukinumab initiation (week 4) lesions in the genital area and patients with skin fold involvement experienced a rapid regression which was evident in 37/44 (84.1%) of patients. Skin folds and genitals were remarkably cleared at week 5 (mean week of clearing 5.29 [SD 1.49], median week of clearing: 5, [IQR:2]), and sPGA 0/1 at week 4. Regarding drug retention, we report 11 patients that had to discontinue treatment throughout the observation period. 7 patients lost PASI75 within more than 2 years of the treatment and lost its effectiveness. 3 patients had to switch to other therapies because they did not respond to the drug by week 16 (Table 3).

Safety
Most of the adverse events (AE) recorded was characterized as low grade and did not require a treatment discontinuation. Actually 3 patients reported AE: two patients reported fatigue grade 1 CTCAE possibly drug-related and one reported headache grade 1 CTCAE probably not-drug related. Four patients had to discontinue the treatment up until week 16 due to lack of efficacy. Lastly, one patient was diagnosed with ulcerative colitis at week 108 and the treatment was discontinued. Up until the 208 weeks of the observation period no major adverse events were recorded.

During the observation period after week 16 and up until week 208, 11 patients discontinued the treatment due to lack of efficacy and this was observed mainly after 104 weeks of therapy, in bio-experienced patients and patients with multiple comorbidities (Table 3).

In three patients a quantiferon tuberculosis conversion was recorded, but a systematic infection was not confirmed. For safety reasons those patients underwent prophylactic antibiotic therapy.

Conclusions
Our study provides retrospective data of patients with chronic plaque psoriasis and their treatment outcomes after receiving secukinumab in real-life clinical practice in Greece. Additionally, we focused on difficult-to-treat areas, namely psoriasis affecting the skin folds and the genital area, mainly because data of the effect of secukinumab on these manifestations are limited. The studied population that was selected were patients with moderate to severe chronic plaque psoriasis that were treated with secukinumab at the recommended dose. Bio-naïve, as well as bio-experienced patients were included. Increased rates of comorbidities were recorded, with almost half of the patients reporting at least one; a factor that generally levels up the difficulty in managing the disease. Secukinumab accomplished to improve the disease burden in an impressively fast manner, with over half of the patients (55.6%) achieving PASI75 and one out of four patients (25.3%) achieving PASI90 at week 4. This improvement continued to increase to reach at week 16 PASI75/PASI90/PASI100 in 87.5%/69.8%/49% respectively.

In accordance with the treatment outcomes of this study, secukinumab has shown high efficacy in managing psoriasis quickly. In fact in ERASURE, FEATURE and JUNCTURE clinical trials there was a PASI75/PASI90/PASI100 reduction rate at week 16 in 86.1%/69.8%/41.6% [5]. Similar were the results from Rompoti et al in Greece where, at week 16, a PASI75/PASI90/PASI100 reduction rate in 83.3%/70%/46.3% of the patients was recorded [6]. Our study population shares some characteristics with the above-mentioned study in Greece. Namely both include overweight patients (mean BMI: 29.3; range: 18.4-45.2 versus 29.1; range: 17.3-50.2) and almost half of the studied population in both trials have at least one comorbidity (46% versus 49.4%). We report 32.3% patients with PsA whereas Rompoti et al report 43.2% (versus 20% in clinical trials). Bai et al conducted a systematic review with a network meta-analysis (NMA) of all randomized trials in order to determine the differences in efficacy and safety profiles of IL-17,

Original Article | Dermatol Pract Concept. 2024;14(2):e2024119
Sustained until the end of the observation period (week 208). These findings are in agreement with clinical trials reporting 5-year data, as well as other long-term real-life studies for Secukinumab [8-10].

Addressing the difficult-to-treat psoriatic manifestations, in particular scalp psoriasis, nail psoriasis and palmoplantar psoriasis, secukinumab has shown a rapid and sustained response in improving psoriatic lesions and associated symptoms [11-15]. Likewise treatment response in our studied population showed significant improvement in difficult-to-treat specific locations. We recorded scalp involvement in 74.74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (versa) in 17% (17/99). After secukinumab initiation lesions in the genital area and patients with skin fold involvement experienced a rapid regression which was evident in 37/44 (84.1%) of patients. Skin folds and genitals were remarkably cleared at week 5 (mean 5.29 [SD 1.49], median: 5, [IQR:2]), and sPGA 0/1 at week 4. Data regarding secukinumab efficacy on areas with fold involvement as well as genital psoriasis are lacking from the drug clinical program, as well as the real-world setting. To our knowledge this is the first study that included skin fold improvement as a treatment endpoint for investigating the treatment efficacy of secukinumab in this difficult-to-treat area. However, patients of this study who had chronic plaque psoriasis and lesions affecting the skin folds and the genital area could be characterized as IL12/23 and IL23 inhibitors used in treating moderate to severe plaque psoriasis. Regarding the short-term achievements amongst 19840 patients from 28 trials secukinumab ranked first in achieving sPGA 0/1 or IGA 0/1 or PGA 0/1, and second in achieving PASI75 at week 12 or 16 [7]. In agreement with that, and according to the results of our study, secukinumab is highly efficacious in managing the disease burden of chronic plaque psoriasis in a fast manner in real life clinical practice too. In phase II/III, clinical trials patients are selected according to specific inclusion criteria. It is reasonable to hypothesize that in a real-world setting, where patients differ at least in disease severity and comorbidities, treatment efficacy can vary vastly. Augustin et al designed a review of all available published studies of real-world evidence using secukinumab in treating plaque psoriasis from 1 January 2015 to 31 May 2019. This meta-analysis included 43 studies and the effectiveness results for PASI75/PASI90/ PASI100 at 12 weeks were 72%/50%/36% respectively. The endpoint of clinical improvement of psoriasis in our real-life population complies with this data, supporting additionally the consistency secukinumab offers in fast treatment efficacy.

With regard to the durability of response, secukinumab presented long-lasting and went as far to improve the efficacy at subsequent timepoints in this study, with almost 100% of patients maintaining PASI 75 response, 78.2% achieving PASI 90 response and 47.3% achieving PASI 100 response at week 104, whilst these efficacy rates were further sustained until the end of the observation period (week 208). These findings are in agreement with clinical trials reporting 5-year data, as well as other long-term real-life studies for Secukinumab [8-10].

Addressing the difficult-to-treat psoriatic manifestations, in particular scalp psoriasis, nail psoriasis and palmoplantar psoriasis, secukinumab has shown a rapid and sustained response in improving psoriatic lesions and associated symptoms [11-15]. Likewise treatment response in our studied population showed significant improvement in difficult-to-treat specific locations. We recorded scalp involvement in 74.74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (versa) in 17% (17/99). After secukinumab initiation lesions in the genital area and patients with skin fold involvement experienced a rapid regression which was evident in 37/44 (84.1%) of patients. Skin folds and genitals were remarkably cleared at week 5 (mean 5.29 [SD 1.49], median: 5, [IQR:2]), and sPGA 0/1 at week 4. Data regarding secukinumab efficacy on areas with fold involvement as well as genital psoriasis are lacking from the drug clinical program, as well as the real-world setting. To our knowledge this is the first study that included skin fold improvement as a treatment endpoint for investigating the treatment efficacy of secukinumab in this difficult-to-treat area. However, patients of this study who had chronic plaque psoriasis and lesions affecting the skin folds and the genital area could be characterized as

---

### Table 3. Previous treatment, Adjuvant therapy, reason for discontinuation.

<table>
<thead>
<tr>
<th>Patient (gender, age)</th>
<th>Previous treatment</th>
<th>Adjuvant therapy</th>
<th>Week of treatment</th>
<th>Reason for discontinuation</th>
<th>Discontinuation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, 76y</td>
<td>acitretin</td>
<td>Week 52</td>
<td>Loss of effectiveness</td>
<td>Week 80</td>
<td></td>
</tr>
<tr>
<td>Male, 49y</td>
<td>Ustekinumab</td>
<td>Topical steroids</td>
<td>Week 24</td>
<td>Loss of effectiveness</td>
<td>Week 52</td>
</tr>
<tr>
<td>Male, 55y</td>
<td>Infliximab, Ustekinumab</td>
<td>Topical steroids</td>
<td>Week 48</td>
<td>Loss of effectiveness</td>
<td>Week 112</td>
</tr>
<tr>
<td>Male, 52y</td>
<td>Topical steroids</td>
<td>Week 108</td>
<td>Loss of effectiveness</td>
<td>Week 160</td>
<td></td>
</tr>
<tr>
<td>Male, 31y</td>
<td>Cyclosporine</td>
<td>Topical steroids</td>
<td>Week 52</td>
<td>Loss of effectiveness</td>
<td>Week 108</td>
</tr>
<tr>
<td>Female, 59y</td>
<td>Cyclosporine, Infliximab Methotrexate, Apremilast</td>
<td></td>
<td>Loss of effectiveness</td>
<td>Week 70</td>
<td></td>
</tr>
<tr>
<td>Female, 53y</td>
<td>Cyclosporine, Acitretin</td>
<td>Topical steroids</td>
<td>Week 52</td>
<td>Loss of effectiveness</td>
<td>Week 120</td>
</tr>
<tr>
<td>Male, 55y</td>
<td>Ustekinumab, Adalimumab</td>
<td></td>
<td>No response</td>
<td>Week 16</td>
<td></td>
</tr>
<tr>
<td>Female, 47</td>
<td>Ustekinumab, Adalimumab</td>
<td></td>
<td>No response</td>
<td>Week 16</td>
<td></td>
</tr>
<tr>
<td>Male, 52y</td>
<td>Cyclosporine, Infliximab, Adalimumab, Methotrexate</td>
<td>Methotrexate</td>
<td>Week 0</td>
<td>No response</td>
<td>Week 20</td>
</tr>
<tr>
<td>Male, 42y</td>
<td></td>
<td></td>
<td>Ulcerative colitis</td>
<td>Week 152</td>
<td></td>
</tr>
</tbody>
</table>

---

IL12/23 and IL23 inhibitors used in treating moderate to severe plaque psoriasis. Regarding the short-term achievements amongst 19840 patients from 28 trials secukinumab ranked first in achieving sPGA 0/1 or IGA 0/1 or PGA 0/1, and second in achieving PASI75 at week 12 or 16 [7].

In agreement with that, and according to the results of our study, secukinumab is highly efficacious in managing the disease burden of chronic plaque psoriasis in a fast manner in real life clinical practice too. In phase II/III, clinical trials patients are selected according to specific inclusion criteria. It is reasonable to hypothesize that in a real-world setting, where patients differ at least in disease severity and comorbidities, treatment efficacy can vary vastly. Augustin et al designed a review of all available published studies of real-world evidence using secukinumab in treating plaque psoriasis from 1 January 2015 to 31 May 2019. This meta-analysis included 43 studies and the effectiveness results for PASI75/PASI90/ PASI100 at 12 weeks were 72%/50%/36% respectively. The endpoint of clinical improvement of psoriasis in our real-life population complies with this data, supporting additionally the consistency secukinumab offers in fast treatment efficacy.

With regard to the durability of response, secukinumab presented long-lasting and went as far to improve the efficacy at subsequent timepoints in this study, with almost 100% of patients maintaining PASI 75 response, 78.2% achieving PASI 90 response and 47.3% achieving PASI 100 response at week 104, whilst these efficacy rates were further sustained until the end of the observation period (week 208). These findings are in agreement with clinical trials reporting 5-year data, as well as other long-term real-life studies for Secukinumab [8-10].

Addressing the difficult-to-treat psoriatic manifestations, in particular scalp psoriasis, nail psoriasis and palmoplantar psoriasis, secukinumab has shown a rapid and sustained response in improving psoriatic lesions and associated symptoms [11-15]. Likewise treatment response in our studied population showed significant improvement in difficult-to-treat specific locations. We recorded scalp involvement in 74.74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (psoriasis inversa) in 17% (17/99). After secukinumab initiation lesions in the genital area and patients with skin fold involvement experienced a rapid regression which was evident in 37/44 (84.1%) of patients. Skin folds and genitals were remarkably cleared at week 5 (mean 5.29 [SD 1.49], median: 5, [IQR:2]), and sPGA 0/1 at week 4. Data regarding secukinumab efficacy on areas with fold involvement as well as genital psoriasis are lacking from the drug clinical program, as well as the real-world setting. To our knowledge this is the first study that included skin fold improvement as a treatment endpoint for investigating the treatment efficacy of secukinumab in this difficult-to-treat area. However, patients of this study who had chronic plaque psoriasis and lesions affecting the skin folds and the genital area could be characterized as...
secondary involvement. Burlando et al recently presented the superiority of anti-IL17 antibodies, in comparison to anti-IL12/23 and anti-TNFα drugs, in improving genital psoriasis in a small group of female patients [16].

With regard to drug retention, we report only 11 patients that had to discontinue the treatment. Seven patients lost PASI75 within more than 2 years of treatment and lost its effectiveness. Three patients had to switch to other therapies because they did not respond to the drug by week 16 (Table 3). These results adhere to what has been presented in other real-world studies assessing psoriasis patients treated with Secukinumab [6,10,17]. Additionally, it needs to be mentioned that, in our study, almost half of the patients who discontinued secukinumab (5/11, 45%) were bio-experienced with at least one biologic drug that failed in the management of the disease. Previous biologic experience has been already identified as a factor influencing drug survival [18].

Another key point to be mentioned is the fact that in January 2022, the local label of Secukinumab was updated to include an intensified dosing scheme (300 mg every 2 weeks, as maintenance dose) for adult patients with moderate to severe plaque psoriasis and body weight 90 kg or higher, based on clinical response. Since the observation period of this study started before this update, it is not known, whether the efficacy outcomes in patients who belong to this sub-population and show a sub-optimal response could have responded better, had this option been available at the time [19].

Treatment with secukinumab during the 208 weeks of observation did not reveal any major adverse events or systemic infections and it was generally well-tolerated. Only three patients reported AEs of low grade, which at no point was an adequate enough reason to discontinue secukinumab. These were characterized as self-limited without requiring any additional treatment.

One 42-year-old male patient was diagnosed with ulcerative colitis at week 152 of treatment. Personal and family history were negative of any inflammatory bowel disease, and he was a smoker. This is characterized as a paradoxical gastrointestinal effect of IL-17 inhibitors with a still unclear pathogenetic mechanism. It is believed that type I interferon might be involved and may be the reason for a hyperactive innate inflammatory pathway [20]. Furthermore, three of our patients had a quantifier tuberculosis conversion and as per the guidelines they underwent prophylactic antibiotic therapy without clinical or radiographic evidence of TB infection.

We acknowledge the fact that this is a retrospective monocentric observational study and the data extracted were obtained from a small number of patients. This retrospective nature of this study could also explain the small number of reported AEs extracted from patient records that were used for this analysis.

According to our outcomes, secukinumab is an effective treatment choice for treating chronic plaque psoriasis, but, additionally, it can be efficacious in the subgroups of patients with difficult-to-treat manifestations. Especially, regarding lesions at the genital area, as well as psoriasis inversa, patients in our study experienced a great improvement and this occurred rapidly at a mean time of 5 weeks after therapy initiation. In addition, the already well described advantageous safety profile of secukinumab is confirmed by the results of this study, since we did not report any serious adverse events during the 208 weeks observational period. Consequently, this real-life study offers information about clinical efficacy, retention and safety profile of secukinumab in patients from everyday clinical practice over a long-term, 4-year, follow-up period in Greece.

Acknowledgement: This study was conducted in collaboration with Novartis, Greece.

References


7. B Bai F, Li GG, Liu Q, Niu X, Li R, Ma H. Short-Term Efficacy and Safety of IL-17, IL-12/23, and IL-23 Inhibitors Brodalumab, Secukinumab, Ixekizumab, Ustekinumab, Guselkumab, Tildrakizumab, and Risankizumab for the Treatment of Moderate to Severe Plaque Psoriasis: A Systematic Review and Network...


Efficacy of Long-Pulsed Nd:YAG Laser for Classic Kaposi’s Sarcoma: A Dermoscopic Study

Seher Bostanci¹, Merve Aygun Alizada², Banu Farabi³, Bengu Nisa Akay¹

¹Dermatology and Venerology Department of Ankara University, Ankara, Turkey
²Dermatology Department of Mamak State Hospital, Ankara, Turkey
³Dermatology Department, NYC Health + Hospitals/South Brooklyn Health, NY

Key words: classic Kaposi’s sarcoma, dermoscopy, long-pulsed neodymium-doped yttrium–aluminum–garnet laser, treatment

Citation: Bostanci S, Aygun Alizada M, Farabi B, Akay BN. Efficacy of Long-Pulsed Nd:YAG Laser for Classic Kaposi’s Sarcoma: A Dermoscopic Study. Dermatol Pract Concept. 2024;14(2):e2024150. DOI: https://doi.org/10.5826/dpc.1402a150

Accepted: March 17, 2024; Published: April 2024

Copyright: ©2024 Bostanci et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. M.A.: Study design; conceptualization; methodology; writing; databases strategy research and extraction of data, S.B.: supervision; data curation B.F.: databases strategy research, supervision, B.N.A.: Data curation, study design; methodology; supervision. All authors have read and agreed to the published version of the manuscript.

Corresponding Author: Merve Aygun Alizada, MD, Mamak State Hospital, Department of Dermatology Ankara, Uregil mah, 06230 Mamak/Ankara/Turkey. Telephone: +903573102289 Fax number: +903123108636 E-mail: werve2007@gmail.com

ABSTRACT

Introduction: Classic Kaposi’s sarcoma (CKS) is a chronic and indolent skin tumor. Because CKS has a low mortality rate but can have a significant impact on quality of life, it is important to choose safe, long-term treatments with minimal side effects.

Objectives: The aim was to assess the efficacy of long-pulsed Nd:YAG laser therapy in treating CKS based on clinical and dermoscopic observations.

Methods: Forty-two nodular lesions from three CKS patients (stage 4) were treated using a long-pulsed Nd:YAG laser with a spot size ranging from 3 to 7 mm, a fluence of 200–250 J/cm², and a pulse duration lasting between 10 and 20 milliseconds in one or two sessions. Patients were photographed clinically and dermoscopically before the procedure, immediately after the procedure, and at 1, 6, and 12 months after the procedure.

Results: All participants displayed significant clinical and dermoscopic improvements, and all lesions healed within 2–3 weeks, resulting in only minor atrophic scars. No instance of recurrence was found among any of the patients during the 1-year follow-up.

Conclusions: Nd:YAG laser therapy may prove to be an effective therapeutic alternative for both early and advanced-stage CKS, specifically in instances of stubborn cutaneous lesions or patients receiving systemic therapy. The treatment results in quick improvement, typically within 2–3 weeks, and is well tolerated. Nd:YAG laser therapy could provide potential benefits for HIV-positive patients as it is free from immunosuppression, easy to apply to recurring lesions, and demonstrates overall effectiveness and safety.
Introduction

Classic Kaposi’s sarcoma (CKS) is a chronic indolent angioproliferative skin tumor associated with human herpesvirus 8 (HHV8) and is characterized by violaceous macules, papules, and nodules. The lesions are often located in the lower extremities and include macules, nodules, and plaques, depending on stage of the lesions. CKS predominantly affects males, with a male-to-female ratio of 3:1, with the highest incidence observed in the sixth decade of life [1]. CKS is prevalent in Mediterranean and Eastern European regions, and risk factors are advanced age, immune deficiency, and sexual activity [1]. The definitive diagnosis of CKS relies on histopathological analysis, with clinical and dermoscopic findings playing a crucial role. While CKS has a low mortality rate, it significantly impacts the quality of life of affected individuals [2]. Therefore, it is important to choose a reproducible local treatment that is long-term, fast-acting, and safe and that has minimal side effects in this cutaneous limited disease. Local treatments using various types of lasers have been reported in the literature.

Objective

Here, we aimed to investigate the clinical and dermoscopic features as well as the outcomes of neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser treatment in three CKS patients.

Methods

We evaluated a total of 42 nodular lesions located in the lower and upper extremities of three CKS patients who visited our clinic between March 2018 and January 2020. The retrospective study protocol was approved by our Ethics Committee (Ethics Committee Approval n. 110-701-23), and informed consent was obtained from the patients. All of our patients had been diagnosed pathologically with KS prior to enrolling to this study. The patients had no history of immunosuppressive drug use, systemic disease, or organ transplantation, and their medical histories were unremarkable. The complete blood count, complete metabolic panel, and HIV serology were normal for all patients. None of the patients had endemic, epidemic, or iatrogenic KS. All patients were staged using lymph node ultrasound, thoraco-abdominopelvic computed tomography, and endo-colonoscopy. None of the patients had extracutaneous or mucosal involvement, and all patients had stage 4 CKS according to the classification of Brambilla et al. [3]. The study excluded patients who had received systemic treatments for CKS in the previous months and lesions that had previously undergone local treatments. None of the patients included in the study had a history of hypertrophic scars or coagulation disorders.

All 42 nodular lesions, ranging in diameter from 3 to 12 mm, underwent long-pulsed Nd:YAG laser treatment, administered in one or two sessions. The laser parameters employed during treatments were as follows: spot diameter of 3–7 mm; energy density of 200–250 j/cm²; pulse duration of 10–20 ms. A satisfactory treatment outcome was defined by the grey whitening of the nodular lesions accompanied by a significant popping sound. Patients were instructed to report any severe pain or discomfort experienced during the procedure. Local anesthesia was not administered prior to the procedure.

For selected thick nodular lesions, a second session of long-pulse Nd:YAG laser treatment administered at 4-week intervals. Nikon 1 AW1 camera Apple iPad mini retina were used to image the lesions clinically, and a DermLite DL3N and DermLite DL4 coupled to a Nikon 1 AW1 camera was used for dermoscopic imaging before the procedure, immediately after the procedure, and at 1, 6, and 12 months after the procedure.

Results

The demographic characteristics, skin type, and clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 70 (57–78) years, and the mean disease duration was 6.6 (5–8) years. The clinical findings of the patients before and after treatment are shown in Figure 1, and the dermoscopic findings are shown in Figure 2. All three patients had multiple, slowly progressive, nodular lesions located in the lower and upper extremities, and the patients were considered to have stage 4 disease. Among the patients included in the study, one exhibited lymphedema associated with CKS in the lower extremities (Figure 1, C and D). All patients had previously undergone treatment for their extensive lesions with interferon α-2a, along with local radiation therapy and surgery. However, in the three months before, during, and one year after laser treatment, none of the patients received any systemic or local treatment.

Long-pulsed Nd:YAG laser treatment was successfully administered to a total of 42 nodular lesions, located in the lower and upper extremities, with diameters ranging from 3 to 12 mm. Throughout the treatment sessions, a consistent popping sound was noted, and no bleeding was observed. Following the treatment, a crust formed in the treated area, by a significant popping sound. Patients were instructed to report any severe pain or discomfort experienced during the procedure. Local anesthesia was not administered prior to the procedure.

None of the patients included in the study had a history of hypertrophic scars or coagulation disorders.

All 42 nodular lesions, ranging in diameter from 3 to 12 mm, underwent long-pulsed Nd:YAG laser treatment, administered in one or two sessions. The laser parameters employed during treatments were as follows: spot diameter of 3–7 mm; energy density of 200–250 j/cm²; pulse duration of 10–20 ms. A satisfactory treatment outcome was defined by the grey whitening of the nodular lesions accompanied by a significant popping sound. Patients were instructed to report any severe pain or discomfort experienced during the procedure. Local anesthesia was not administered prior to the procedure.

For selected thick nodular lesions, a second session of long-pulse Nd:YAG laser treatment administered at 4-week intervals. Nikon 1 AW1 camera Apple iPad mini retina were used to image the lesions clinically, and a DermLite DL3N and DermLite DL4 coupled to a Nikon 1 AW1 camera was used for dermoscopic imaging before the procedure, immediately after the procedure, and at 1, 6, and 12 months after the procedure.

We evaluated a total of 42 nodular lesions located in the lower and upper extremities of three CKS patients who visited our clinic between March 2018 and January 2020. The retrospective study protocol was approved by our Ethics Committee (Ethics Committee Approval n. 110-701-23), and informed consent was obtained from the patients. All of our patients had been diagnosed pathologically with KS prior to enrolling to this study. The patients had no history of immunosuppressive drug use, systemic disease, or organ transplantation, and their medical histories were unremarkable. The complete blood count, complete metabolic panel, and HIV serology were normal for all patients. None of the patients had endemic, epidemic, or iatrogenic KS. All patients were staged using lymph node ultrasound, thoraco-abdominopelvic computed tomography, and endo-colonoscopy. None of the patients had extracutaneous or mucosal involvement, and all patients had stage 4 CKS according to the classification of Brambilla et al. [3]. The study excluded patients who had received systemic treatments for CKS in the previous months and lesions that had previously undergone local treatments. None of the patients included in the study had a history of hypertrophic scars or coagulation disorders.

All 42 nodular lesions, ranging in diameter from 3 to 12 mm, underwent long-pulsed Nd:YAG laser treatment, administered in one or two sessions. The laser parameters employed during treatments were as follows: spot diameter of 3–7 mm; energy density of 200–250 j/cm²; pulse duration of 10–20 ms. A satisfactory treatment outcome was defined by the grey whitening of the nodular lesions accompanied by a significant popping sound. Patients were instructed to report any severe pain or discomfort experienced during the procedure. Local anesthesia was not administered prior to the procedure.

For selected thick nodular lesions, a second session of long-pulse Nd:YAG laser treatment administered at 4-week intervals. Nikon 1 AW1 camera Apple iPad mini retina were used to image the lesions clinically, and a DermLite DL3N and DermLite DL4 coupled to a Nikon 1 AW1 camera was used for dermoscopic imaging before the procedure, immediately after the procedure, and at 1, 6, and 12 months after the procedure.
Table 1. Characteristics of Patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Skin Type</th>
<th>Localization / Number of Nodules</th>
<th>Mucous/Lymph Node/Visceral</th>
<th>CKS Stage *</th>
<th>Disease Duration/Previous Treatments**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>F</td>
<td>2</td>
<td>lower-upper extremity / 18</td>
<td>−</td>
<td>4</td>
<td>5 years / excision, radiotherapy, interferon α-2a</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>M</td>
<td>4</td>
<td>lower-upper extremity / 20</td>
<td>− / lymphedema</td>
<td>4</td>
<td>7 years / excision, radiotherapy, interferon α-2a</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>M</td>
<td>4</td>
<td>lower-upper extremity / 14</td>
<td>−</td>
<td>4</td>
<td>8 years / excision, radiotherapy, interferon α-2a</td>
</tr>
</tbody>
</table>

* Classic Kaposi’s sarcoma staging was performed according to the classification of Brambilla et al. [3].
** In the three months prior, during, and one year after laser treatment, none of the patients received any systemic or local treatment. CKS = classic Kaposi’s sarcoma

Figure 1. Clinical manifestations of lesions before and after treatment: (A, B) Regression of multiple red-purple papules with atrophic scar on left upper leg after treatment; (C, D) Regression of red-purple nodules and papules on the right upper leg with atrophic scarring after treatment.
Figure 2. Dermoscopic findings of lesions before and after treatment: (A, B) Regression of nodular lesion with scale consisting of white-blue-pink areas with a polychromatic rainbow pattern and surrounded by a sharply circumscribed brown collarette after treatment; (C) Irregular white clods and a rainbow pattern in a nodular lesion with a pink-white-red polychromatic discoloration surrounded by a yellow-brown color; (D) Atrophic scarring of this lesion after treatment; (E) White clods consisting of white-red-pink areas surrounded by a polychromatic collarette around the hemorrhagic ulcerated area in the central areas of irregular white lines with scale; (F) Mild atrophic scarring of this lesion after treatment.

Discussion

KS, which originates from vascular and lymphatic endothelial structures, is a multisystem disease with prominent skin involvement. Four subtypes of KS have been defined: classic, endemic, iatrogenic, and AIDS-related. In these subtypes, in which systemic involvement is seen at different rates, the prognoses also vary. CKS is characterized by chronic blue-, red-, and purple-colored macular papules, nodules, and plaques in elderly patients, and ulceration, bleeding, and hyperkeratosis can be seen in nodular lesions [2]. Lymphedema is observed in 20% of patients with CKS starting from early-stage disease, and it impairs quality of life [4]. Skin lesions are usually located on the lower extremities, less frequently on the upper extremities, head, and body [3]. Oral, genital, and conjunctival mucosal involvement can be seen, and lymph node and gastrointestinal involvement can be detected in advanced CKS [3]. Along with clinical findings, dermoscopic findings are also very important in the diagnosis and follow-up of the disease [5]. Dermoscopic findings such as blue, purple, and red areas, rainbow pattern, squam on the surface, collar sign, small brown globules, white lines, white globules, and polychromatic discoloration with dotted, coiled, and curved vessels and polychromatic discoloration are very helpful in the diagnosis [5]. During pathological examination, detection of HHV8 + atypical endothelial cell proliferation in dilated
vascular structures and spindle-cell infiltration in the dermis is diagnostic [6].

HHV8, which is responsible for the pathogenesis of CKS, remains in endothelial cells in the latent phase after infection, passes into the lytic phase in certain cases, such as hypoxia, viral infection, and immunosuppression, causing clinical findings of KS [7]. Currently, there is no curative treatment for KS as there is no treatment to eliminate HHV8 infection, and there is no randomized controlled trial for treatment. In the selection of treatment, the individual’s KS subtype, clinical features/extent of lesions, immune system, comorbidities, and symptoms should be considered [2].

Pegylated liposomal doxorubicin, paclitaxel, pomalidomide, etoposide, vinblastine or vincristine, bleomycin, gemcitabine, rapamycin, and antiangiogenic agents are systemic treatments that can be used in the presence of rapidly progressive, visceral involvement, widespread involvement of most of the extremities, and severe lymphedema. However, the use of systemic treatments is limited because of their side effects, and these aggressive treatments should not be given to patients in the early stage with limited skin disease [2, 7]. The primary treatment goals for CKS should be to pursue a palliative approach to alleviate lymphedema, reduce the size of cutaneous lesions, and stop or delay disease progression. For this purpose, local treatments, such as elastocompression, surgical excision, cryotherapy, radiotherapy, and intralesional chemotherapies, should be preferred [3]. Elastocompression can prevent lymphedema and new lesion emergence, and surgical excision can be performed on selected well-circumscribed lesions, but it is not recommended for multiple large lesions with unclear borders, and care should be taken to minimize scarring after the procedure [3, 6, 7]. Minimal surgery such as curettage may be preferred for the treatment of exophytic, oozing, or hemorrhagic multiple nodular lesions [8]. Among local treatments, 6–40 Gy radiotherapy, intralesional bleomycin, doxorubicin, vincristine, and interferon alpha-2a injections can be administered [3]. Intralesional vincristine is notably effective and generally less painful than bleomycin [2, 3]. However, it is important to note potential side effects such as pain, pigmentation changes, and edema. Additionally, less common side effects like infection and necrosis can occur. Furthermore, systemic toxicity may develop, particularly in patients with multiple lesions [2, 3]. Local treatments for CKS include the use of CO2, argon, Q-switched 755-nm Alexandrite, pulsed-dye, and Nd:YAG lasers [9, 10].

The Nd:YAG laser operates at a wavelength of 1064 nm, selectively targeting hemoglobin and deoxyhemoglobin in CKS lesions [11]. By emitting light at this specific wavelength, the laser is able of penetrating deep vascular structures with minimal damage to surrounding tissues, effectively destroying the vascular lesions associated with CKS [9, 11]. Nd:YAG laser represents a safe and effective option for patients with multiple widespread lesions who are unable to undergo systemic treatment. It may even be considered the primary choice for disseminated disease [9].

Our study demonstrated both dermoscopic and clinical evidence of the rapid, effective, and safe outcomes achieved with Nd:YAG laser treatment. In our cohort of three patients with stage 4 CKS, 42 nodular lesions were treated with the Nd:YAG laser in one or two sessions. Aside from mild atrophic scarring, no other side effect was observed in the patients, and there were no recurrences during the 1-year follow-up period. These findings are consistent with studies conducted by Özdemir et al. and Nasca et al., where Nd:YAG laser treatment resulted in healing with mild atrophic scarring, no other side effects, and no recurrence in follow-up periods of six months and one year, respectively [9, 12].

Another study by Silvestri et al. explored the efficacy of Nd:YAG laser treatment in patients with stage 1–2 CKS skin lesions and AIDS-related KS lesions (epidemic form) receiving antiretroviral therapy [10]. The treatment was effective in 80% of the patients, with minimal side effects such as post-inflammatory hyperpigmentation and mild hypotrophic scars [10]. Similar to our findings, Nd:YAG laser therapy was deemed a safe and effective treatment option.

Notably, a reduction in lymphedema has been reported in the literature in two CKS patients following Nd:YAG laser therapy [9, 13]. Consistent with these reports, our study also observed a decrease in lymphedema in one patient. However, it is important to note that the small sample size of our study represents a limitation. This effect may be attributed to the modulation of cytokine balance and increased lymphatic circulation, mediated by tissue hypoxia-induced elevation of VEGF levels [14].

**Conclusions**

In summary, our study, along with previous literature, supports the use of Nd:YAG laser therapy as a rapid, effective, and safe treatment option for CKS. The treatment demonstrates favorable outcomes, with minimal side effects and no recurrence. Additionally, Nd:YAG laser therapy may contribute to reducing lymphedema in CKS patients through its impact on cytokine balance and increased lymphatic circulation [13].

Our study provides evidence of the effectiveness and safety of Nd:YAG laser therapy for stage 4 CKS, supported by dermoscopic findings. Nd:YAG laser treatment can be a valuable therapeutic option for both early- and advanced-stage CKS, particularly in cases of resistant skin lesions or patients...
receiving systemic therapy. The treatment is well tolerated, yielding rapid improvement within 2–3 weeks. Nd:YAG laser therapy may also be beneficial for HIV+ patients due to its immunosuppression-free nature, ease of application for recurrent lesions, and overall effectiveness and safety.

References


Bimekizumab for the Treatment of Plaque Psoriasis with Involvement of Genitalia: A 16-Week Multicenter Real-World Experience — IL PSO (Italian Landscape Psoriasis)

Diego Orsini1, Piergiorgio Malagoli2, Anna Balato3, Luca Bianchi4, Pina Brianti5, Dario Buononato3, Martina Burlando6, Giacomo Caldarola7,8, Anna Campanati9, Elena Campione4, Carlo G. Carrera10, Andrea Carugno11,12, Francesco Cusano13, Paolo Dapavo14, Annunziata Dattola15, Clara De Simone7,8, Valentina Dini16, Maria Esposito17, Maria C. Fargnoli17, Francesca M. Gaiani2, Luigi Gargiulo18,19, Paolo Gisondi20, Alessandro Giunta4, Luciano Ibba18,19, Claudia Lasagni21, Francesco Loconsole22, Vincenzo Maione23, Edoardo Mortato22, Angelo V. Marzano10,24, Martina Maurelli20, Matteo Megna25, Santo R. Mercuri5,19, Alessandra Narcisi18, Annamaria Offidani10, Giovanni Paolino5, Aurora Parodi6, Giovanni Pellacani15, Luca Potestio25, Pietro Quaglino14, Antonio G. Richetta15, Francesca Romano27, Paolo Sena11, Marina Venturini23, Chiara Assorgi1,25, Antonio Costanzo18,19

1 Clinical Dermatology Unit, San Gallicano Dermatological Institute IRCCS, Rome, Italy
2 Department of Dermatology, Dermatology Unit Azienda Ospedaliera San Donato Milanese, Milan, Italy
3 Dermatology Unit, University of Campania L. Vanvitelli, Naples, Italy
4 Dermatology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
5 Unit of Dermatology and Cosmetology, IRCCS San Raffaele Scientific Institute, Milan, Italy
6 Section of Dermatology, Department of Health Sciences (DISSAL), IRCCS San Martino University Hospital, Genoa, Italy
7 Section of Dermatology, Department of Translational Medicine and Surgery, Catholic University of the Sacred Heart, Rome, Italy
8 Dermatology Unit, Agostino Gemelli University Polyclinic Foundation, IRCCS, Rome, Italy
9 Department of Clinical and Molecular Sciences - Dermatological Clinic, Università Politecnica delle Marche, Ancona, Italy
10 Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
11 Dermatology Unit, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy
12 Molecular and Translational Medicine (DIMET), University of Milan-Bicocca, Milan, Italy
13 Department of Dermatology, Gaetano Rummo Hospital, Benevento, Italy
14 Department of Biomedical Science and Human Oncology, Second Dermatologic Clinic, University of Turin, Turin, Italy
15 Dermatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Science, University of La Sapienza, Rome, Italy
16 Dermatology Unit, Department of Clinical and Experimental Medicine, Ospedale Santa Chiara, Pisa, Italy
17 Dermatology, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy
18 Dermatology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
19 Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
20 Department of Medicine, Section of Dermatology and Venereology, University of Verona, Verona, Italy
21 Dermatological Clinic, Department of Specialized Medicine, University of Modena, Modena, Italy
22 Department of Dermatology, University of Bari, Bari, Italy
23 Department of Dermatology, ASST Spedali Civili Hospital, Brescia, Italy
24 Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy
25 Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
26 Università Vita-Salute San Raffaele, Milan, Italy
27 Dermatology Unit, AORN “A. Cardarelli”, Naples, Italy
ABSTRACT

Introduction: Genital involvement is observed in approximately 60% of patients with psoriasis, presenting clinicians with formidable challenges in treatment. While new biologic drugs have emerged as safe and effective options for managing psoriasis, their efficacy in challenging-to-treat areas remains inadequately explored. Intriguingly, studies have shown that interleukin (IL)-17 inhibitors exhibit effectiveness in addressing genital psoriasis.

Objectives: We aimed to determine the effectiveness profile of bimekizumab in patients affected by moderate-to-severe plaque psoriasis with involvement of genitalia.

Methods: Bimekizumab, a dual inhibitor of both IL-17A and IL-17F, was the focus of our 16-week study, demonstrating highly favorable outcomes for patients with genital psoriasis. The effectiveness of bimekizumab was evaluated in terms of improvement in Static Physician Global Assessment of Genitalia (sPGA-G) and Psoriasis Area and Severity Index.

Results: Sixty-five adult patients were enrolled. Remarkably, 98.4% of our participants achieved a clear sPGA-G score (s-PGA-g = 0) within 16 weeks. Moreover, consistent improvements were observed in Psoriasis Area and Severity Index scores, accompanied by a significant reduction in the mean Dermatology Life Quality Index, signifying enhanced quality of life. Notably, none of the patients reported a severe impairment in their quality of life after 16 weeks of treatment. In our cohort of 65 patients, subgroup analyses unveiled that the effectiveness of bimekizumab remained unaffected by prior exposure to other biologics or by obesity.

Conclusions: Our initial findings suggest that bimekizumab may serve as a valuable treatment option for genital psoriasis. Nevertheless, further research with larger sample sizes and longer-term follow-up is imperative to conclusively validate these results.
Acknowledgements: Editorial assistance was provided by Luca Giacomelli, PhD, Valeria Benedusi, PhD, Aashni Shah and Valentina Attanasio (Polistudium SRL, Milan, Italy). This assistance was supported by internal funds.

Ethics Statement: Institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. All included patients had provided written consent for retrospective study of data collected during routine clinical practice (demographics, clinical scores). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

Introduction

Genital involvement occurs in over 60% of psoriasis patients throughout the course of their illness [1-3]. This condition is associated with a major impact to quality of life (QoL), since it causes intense burning and pruritus, and is associated with embarrassment in engaging sexual intercourses significantly impacting their quality of life [4-6]. Nevertheless, genital psoriasis is hardly diagnosed in clinical practice and its treatment poses challenges due to its classification as a ‘difficult-to-treat’ area [7]. Indeed, only 40% of patients reported to have had a previous examination of the genital area, and therefore treatment is often initiated late [3].

Topical treatments, predominantly corticosteroids, are the initial choice for mild-to-moderate genital psoriasis [5]. However, the long-term use of corticosteroids is associated with adverse effects, and limited data exist on the efficacy of immunomodulators or vitamin D derivatives in this context [8]. Systemic treatments are considered for moderate-to-severe cases, yet evidence for these therapies remains limited [5,7-10]. Monoclonal antibodies targeting key cytokines in psoriasis pathogenesis, primarily interleukin (IL)-23 and IL-17A, have been developed. While drugs like secukinumab and ixekizumab target IL-17A, brodalumab antagonizes the IL-17A receptor [11,12]. Ixekizumab has shown significant efficacy in treating genital psoriasis, providing consistent and lasting improvements [7,10,13-18]. Recent research has also emphasized the role of IL-17F, which exhibits overlapping pro-inflammatory functions with IL-17A and is more abundant in psoriatic lesions [19]. Bimekizumab, a humanized monoclonal antibody targeting both IL-17A and IL-17F, has gained approval for moderate-to-severe plaque psoriasis treatment following four successful phase-III clinical trials (BE READY, BE VIVID, BE SURE; BE RADIANT) demonstrating its superior efficacy compared to placebo, ustekinumab, adalimumab, and secukinumab [20-23].

Despite these achievements, real-world data on bimekizumab are limited to case reports and a recent retrospective multicenter study by Gargiulo et al [24-26]. However, no data are currently available regarding the effectiveness of bimekizumab on difficult-to-treat areas, and genitalia in particular. Given ixekizumab high efficacy in treating psoriatic lesions and the increased odds of genital psoriasis clearance with anti-IL-17A inhibitors, as demonstrated in a recent prospective observational study, coupled with the prevalence of IL-17F in psoriatic lesions, we undertook this study to explore the effectiveness of bimekizumab specifically in this challenging-to-treat body area [19,27].

Objectives

In this paper, we present the results of a retrospective observational multicenter study with a 16-week follow-up period, aiming to assess the effectiveness of bimekizumab in the treatment of genital psoriasis.

Methods

This was a retrospective, observational multicenter study conducted at 20 Italian Dermatology Clinics, from January 2023 to August 2023. Consecutive adult (≥18 years) patients with moderate-to-severe plaque psoriasis involving the genital area were eligible for inclusion in this study if they received treatment with bimekizumab. Patients eligibility for bimekizumab treatment was assessed in accordance with the Italian Guidelines as outlined by Gisondi et al in 2022 [28].

Definition of Genital Involvement

To differentiate genital psoriasis from inverse psoriasis, we defined genital involvement based on specific anatomical regions. For males, genital involvement encompassed lesions on the pubis, shaft, foreskin, glans, scrotum, and perineum [7]. For females, it included lesions on the mons pubis, labia majora, labia minora, anterior commissure, interlabial groove, and perineum [7]. Patients with lesions in the inguinal folds and intergluteal cleft but without involvement in the aforementioned anatomical sites were excluded from the study [7].

All patients received bimekizumab in accordance with the Summary of Product Characteristics [29]. They were followed up until week 16, receiving two subcutaneous injections of 160 mg each at weeks 0, 4, 8, 12, 16 [29]. No concurrent topical or systemic agents were administered in conjunction with bimekizumab treatment.

Ethical Considerations

This study adhered to established clinical standards and did not require approval from the institutional review board.
All patients provided written consent for the retrospective collection of their anonymous data. The research was conducted in compliance with the Helsinki Declaration of 1964 and its subsequent amendments.

Assessment
In accordance with our institution standard protocol, assessments of effectiveness and safety were conducted at baseline, week 4, and week 16. During each dermatological examination, the following parameters were evaluated:

i. Static Physician Global Assessment of Genitalia (sPGA-G): this clinician-reported outcome measure, developed specifically for grading the severity of genital psoriasis, assesses erythema, plaque elevation, and scaling on a 6-point scale (0: clear; 5: very severe) [6].

ii. Psoriasis Area and Severity Index (PASI) score: including PASI75, PASI90, and PASI100 (percentages of patients who achieved a percentage reduction of 75%, 90%, and 100% from baseline, respectively).

iii. Proportion of patients achieving an absolute PASI of 2 or less at each visit.

iv. Dermatology-Life-Quality-Index (DLQI).

v. Percentage of patients with DLQI≥10 (indicating a severe impact on quality of life).

Data Analysis
Data analysis was conducted utilizing descriptive statistics. Continuous variables were presented as the mean and standard deviation (SD), while categorical variables were represented as the absolute number and percentage. To assess differences between baseline and follow-up visits, the Wilcoxon matched-pair rank test was employed. A P value less than 0.05 was considered statistically significant. Subgroup analyses were performed to assess the impact of previous exposure to other biologics and the presence of obesity as a comorbidity on the effectiveness of bimekizumab. All analyses were carried out using GraphPad Prism software v8.0.

Results
Patient Population
A total of 65 patients were enrolled in this study, with 46 of them being males (70.8%). The average age of the patients was 50.4±14.2 years. Detailed demographic characteristics and clinical features of all patients at baseline are presented in Table 1. The mean body mass index (BMI) among the patients was 26.7±5.6 kg/m². Fourteen patients were obese (21.5%), with a BMI ≥30. Additionally, 6 patients (9.2%) had a concomitant diagnosis of psoriatic arthritis. Approximately 3/4 of the patients (74.6%) had at least one cardio-metabolic comorbidity, which included conditions such as obesity, arterial hypertension, cardiovascular disease, type II diabetes mellitus, and hyperlipidemia. Interestingly, 19 patients (29.2%) had experienced a previous SARS-CoV-2 infection. The patients had a mean history of psoriasis of 13.9±11.3 years. At baseline, the mean PASI was 18.3±9.0, indicating the severity of psoriasis. DLQI at baseline had an average score of 17.1±8.8, highlighting a substantial impact on the quality of life for these patients. Fifty-one patients reported a severe impairment of their quality of life, with a DLQI score of ≥10 (81%). Twenty-five patients had previously failed at least one biological therapy (38.5%), while

Table 1. Demographics and General Clinical Characteristics of Patients With Genital Psoriasis at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.4 (14.2%)</td>
</tr>
<tr>
<td>Male sex</td>
<td>46 (70.8%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 (5.6%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>• Psoriatic Arthritis</td>
<td>6 (9.2%)</td>
</tr>
<tr>
<td>• Obesity</td>
<td>14 (21.5%)</td>
</tr>
<tr>
<td>• Type 2 diabetes</td>
<td>5 (7.7%)</td>
</tr>
<tr>
<td>• Hyperlipidemia</td>
<td>10 (15.4%)</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>15 (23.1%)</td>
</tr>
<tr>
<td>• Cardiovascular diseases</td>
<td>3 (4.6%)</td>
</tr>
<tr>
<td>Previous SARS-CoV-2 infection</td>
<td>19 (29.2%)</td>
</tr>
<tr>
<td>Mean age at baseline (years)</td>
<td>48.2 (14.9)</td>
</tr>
<tr>
<td>Mean duration of psoriasis (years)</td>
<td>13.9 (11.3)</td>
</tr>
<tr>
<td>Psoriasis on special locations</td>
<td></td>
</tr>
<tr>
<td>• Genital</td>
<td>65 (100%)</td>
</tr>
<tr>
<td>• Scalp</td>
<td>48 (73.8%)</td>
</tr>
<tr>
<td>• Palmo-plantar</td>
<td>19 (29.2%)</td>
</tr>
<tr>
<td>• Nails</td>
<td>25 (38.5%)</td>
</tr>
<tr>
<td>Mean PASI at baseline</td>
<td>18.3 (9.0%)</td>
</tr>
<tr>
<td>Mean DLQI at baseline</td>
<td>17.1 (8.8%)</td>
</tr>
<tr>
<td>Previous exposure to biologics</td>
<td>25 (38.5%)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12 (18.5%)</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Risankizumab</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>9 (13.8%)</td>
</tr>
<tr>
<td>Tildrakizumab</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>3 (4.6%)</td>
</tr>
</tbody>
</table>

BMI = body mass index; DLQI = Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index.

PASI and DLQI scores were available for 63 patients at baseline. Continuous variables were reported as mean (standard deviation), while categorical variables were expressed as absolute number (percentage).
At baseline, PASI was recorded for 63 patients, and 61 of them completed 16 weeks of follow-up. In our study, there was a notable increase in the percentage of patients achieving PASI75, PASI90, and PASI100 between the 4-week and 16-week marks of bimekizumab treatment (Figure 2). Specifically, PASI75 was achieved by 43 patients after 4 weeks (70.5%) and by 57 patients after 16 weeks (93.4%) (Figure 2). Additionally, PASI90 increased from 29 patients at 4 weeks (47.5%) to 48 patients at 16 weeks (78.7%). The percentage of patients achieving PASI100 increased from 25 at 4 weeks (41%) to 42 after 16 weeks of treatment (68.9%) (Figure 2).

The mean PASI decreased significantly from 18.3±9.0 at baseline to 4.3±13 after 4 weeks of treatment (P < 0.001) and 38 patients were bio-naive (61.5%) (Table 1). A significant proportion of patients, specifically 63 out of 65 (96.9%), successfully completed the 16-week treatment course. The remaining patients were lost to follow-up.

**Effectiveness Assessment**

At baseline, more than half of the patients had a moderate-to-severe genital involvement, defined as a s-PGA-G of 3 or more (Figure 1 and Table 2). Among the 63 patients evaluated for sPGA-G at the 4-week mark, 48 patients achieved a sPGA-G score of clear (76.2%), while 11 patients achieved a score of almost clear (17.5%). Impressively, at the 16-week visit, 98.4% of the assessed patients had achieved a sPGA-G score of clear, demonstrating the remarkable efficacy of bimekizumab in clearing genital psoriasis (Figure 1, Table 2).

**PASI Improvement**

At baseline, PASI was recorded for 63 patients, and 61 of them completed 16 weeks of follow-up. In our study, there was a notable increase in the percentage of patients achieving PASI75, PASI90, and PASI100 between the 4-week and 16-week marks of bimekizumab treatment (Figure 2). Specifically, PASI75 was achieved by 43 patients after 4 weeks (70.5%) and by 57 patients after 16 weeks (93.4%) (Figure 2). Additionally, PASI90 increased from 29 patients at 4 weeks (47.5%) to 48 patients at 16 weeks (78.7%). The percentage of patients achieving PASI100 increased from 25 at 4 weeks (41%) to 42 after 16 weeks of treatment (68.9%) (Figure 2).

The mean PASI decreased significantly from 18.3±9.0 at baseline to 4.3±13 after 4 weeks of treatment (P < 0.001) and

---

![Image of Figure 1: Static genital PGA score (Static Physician Global Assessment of Genitalia, sPGA-G) distribution over time. Data were expressed as absolute number (percentage).](image)

![Image of Table 2: Static Genital PGA score (sPGA-G) distribution over time.](image)

<table>
<thead>
<tr>
<th>sPGA-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (N = 65)</td>
</tr>
<tr>
<td>Clear</td>
</tr>
<tr>
<td>Almost clear</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Very severe</td>
</tr>
</tbody>
</table>

sPGA-G = Static Physician Global Assessment of Genitalia.
from 51 patients (81%) at baseline to 5 patients (8.3%) after 4 weeks of treatment. None of the patients had a DLQI≥10 after 16 weeks of treatment (Table 3).

Given the impressive response of genital psoriasis to bimekizumab in almost all of our patient, in our study we found no significant impact of prior biologics exposure on the improvement of sPGA-G or on the likelihood of achieving PASI75, PASI90, or PASI100 during the study (Figure 3). Similarly, the presence of obesity as a comorbidity did not appear to have a statistically significant effect on the bimekizumab-induced improvement of sPGA-G values. Obesity did not significantly influence the likelihood of achieving PASI75, PASI90, or PASI100 during the study (Figure 3). These findings suggest that bimekizumab is effective in improving genital psoriasis and associated quality of life, regardless of prior biologic exposure or the presence of obesity as a comorbidity.

Conclusions
To date, no specific guidelines are available regarding the treatment of genital psoriasis with biological drugs. However, a few real-world experiences have been recently

Figure 2. Percentage of patients achieving Psoriasis Area and Severity Index (PASI) 75, PASI90 and PASI 100 over time. Baseline, N = 63; week 4, N = 61; week 16, N = 61; PASI75, at least a 75% improvement from baseline in PASI; PASI90, at least a 90% improvement from baseline in PASI PASI100, 100% improvement from baseline in PASI. PASI score was available for 63 patients at baseline and for 61 patients at weeks 4 and 16.

Table 3. Mean PASI and DLQI, Percentage of Patients with PASI≤2, and Percentage With DLQI≥10 Over Time.

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean PASI</th>
<th>PASI≤2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>18.3 (9.0)</td>
<td>-</td>
</tr>
<tr>
<td>4 weeks</td>
<td>4.3 (13.0)</td>
<td>28 (46.7%)</td>
</tr>
<tr>
<td>16 weeks</td>
<td>1.1 (3.5)</td>
<td>47 (78.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean DLQI</th>
<th>DLQI ≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>17.1 (8.8)</td>
<td>51 (81.0%)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>2.9 (4.0)</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td>16 weeks</td>
<td>0.5 (1.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

was further reduced to 1.1±3.5 after 16 weeks of therapy (P < 0.001) (Table 3). At baseline, only 1 patient (1.6%) had a PASI score < 2, while 28 patients (46.7%) and 47 patients (78.3%) had a PASI score < 2 after 4 weeks and 16 weeks of treatment, respectively (Table 3).

DLQI Improvement
At baseline, DLQI scores were available for 63 patients and 61 of them had a 4- and 16-week follow-up. The rapid improvement in PASI scores was paralleled by a decrease in the mean DLQI throughout the study period (Table 3). The DLQI, which was 17.1±8.8 at baseline, significantly improved to 2.9±4 at 4 weeks (P < 0.001, paired sample t-test) and further dropped to 0.5±1.4 at 16 weeks (P < 0.001, paired sample t-test). The number of patients reporting severe impairment of quality of life (DLQI ≥10) decreased
published on the role of anti-IL-23 and anti-IL17A drugs [16,30]. Real-world evidence on the effectiveness of bimekizumab in this subset of patients are extremely limited.

When examining our study population at baseline, we observed similarities in their characteristics when compared to the participants in phase-3 clinical trials evaluating bimekizumab in psoriatic patients [20-23]. One notable exception was the lower mean PASI at baseline in our study. This discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].

The data presented in our study highlight the remarkable effectiveness of bimekizumab in the treatment of genital psoriasis. We observed rapid and significant improvements in the severity of genital psoriasis, as measured by the sPGA-G score, with 98.4% of patients achieving a clear sPGA-G score after just 16 weeks of treatment.

Compared with ixekizumab, the only biological treatment specifically approved for genital psoriasis treatment, we observed better clinical responses at week 16 [31]. As a matter of fact, the study on ixekizumab by Guenther et al showed that 75% of patients achieved a clear or almost clear sPGA-G score after 52 weeks of treatment, with 60% achieving complete clearance [10]. Similarly, Sotiropoulos et al achieved a sPGA-G score of almost clear or clear in 68.8% and 93.8% of patients treated with ixekizumab at weeks 16 and 24, respectively [16]. These findings suggest that bimekizumab may lead to a more rapid and effective improvement in genital psoriasis compared to ixekizumab, but head-to-head comparison studies are needed to confirm this observation. Our findings could also be partially explained with a moderate discrepancy can be attributed to the stringent inclusion criteria typically employed in clinical trials. Of particular interest, our patients exhibited a higher mean DLQI compared to those involved in the aforementioned trials, underscoring the substantial impact of psoriasis on our patients quality of life [20-23].
been explored yet, thus our study provides initial real-world data, even though they are limited by a small sample size and a relatively short observation period.

In this study, a 16-week course of bimekizumab treatment demonstrated highly favorable outcomes for patients with genital psoriasis. Notably, 98.4% of patients achieved a clear sPGA-G score within 16 weeks of treatment, and there were consistent improvements in PASI scores over the 4 to 16-week treatment period. Furthermore, the study revealed a significant reduction in the mean DLQI score, indicating an improvement in patients quality of life. Noteworthy is the low number of patients reporting severe impairment in quality of life (DLQI ≥10) after only four weeks of treatment, with none experiencing this level of impairment by the end of the 16-week period.

Contrary to some existing literature, our study did not observe differences on the effectiveness of bimekizumab between bio-naïve and bio-experienced subgroups or between non-obese and obese patient groups. It is important to acknowledge the limitations of our study, primarily the relatively small cohort size, which may have influenced these findings.

In summary, our preliminary findings are promising and suggest that bimekizumab holds great potential as a treatment option for genital psoriasis. However, further research with larger sample sizes and longer-term follow-up is essential to validate these results conclusively.

References


18. Soung J, Jennifer CC, Goodeham M. 33054 Improvement in Quality of Life in Patients with Genital Psoriasis Treated with Ixekizumab: 52-Week Results of a Phase 3 Clinical Trial in Patients with Moderate-to-Severe Genital Psoriasis (IXORA-Q).


Long-Term Effectiveness of Brodalumab for the Treatment of Moderate-To-Severe Psoriasis: A Real-Life Multicenter Study of Up to 3 Years in a Real-Life Italian Cohort

Giacomo Caldarola1,2, Marco Galluzzo3,4, Nicoletta Bernardini5, Elisabetta Botti4, Eleonora De Luca1,2, Clara De Simone1,2, Marco Mariani6, Gaia Moretta7, Sabatino Pallotta7, Elena Campione3,4, Ketty Peris1,2

1 UOC di Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy
2 Dermatologia, Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy
3 Department of Systems Medicine, University of Rome “Tor Vergata”, Rome, Italy
4 Dermatology Unit, Azienda Ospedaliera Universitaria “Policlinico Tor Vergata”, Rome, Italy
5 Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University Dermatology Unit “Daniele Innocenzi”, ASL Latina, Italy
6 Section of Hygiene, University Department of Health Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy
7 Dermatology Unit, Istituto Dermopatico dell’Immacolata IDI-IRCCS, Rome, Italy

Key words: biologics, brodalumab, drug survival, IL-17 inhibitors, psoriasis, real-life effectiveness

DOI: https://doi.org/10.5826/dpc.1402a152
Accepted: April 15, 2024; Published: April 2024

Copyright: ©2024 Caldarola et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: G Caldarola has received consulting fees, honoraria and support for attending meetings from Abbvie, Lilly, Janssen, UCB, Novartis and Leopharma; C De Simone has received support for consulting fees, honoraria and support for attending meetings from Abbvie, Lilly, Janssen, UCB, Novartis, Leopharma, Sanofi and Almirall; K Peris has received support for consulting fees and honoraria from Abbvie, Almirall, Biogen, Celgene, Janssen Galderma, Novartis, Lilly, Novartis, Pierre Fabre, Sandoz, Sanofi and Sun Pharma. M Galluzzo declare to have acted as speakers and/or consultants for AbbVie, Almirall, Eli-Lilly, Janssen-Cilag, Leop Pharma, Novartis and Sanofi, outside the submitted work. E Campione served as a consultant for Almirall, BMS, Amgen, and UCB. G Moretta has received consulting fees, honoraria and support for attending meetings from Abbvie, Leopharma, Sanofi and Lilly. All other authors declare that they have no conflicts of interest relevant to this manuscript.

Authorship: G. Caldarola and M. Galluzzo contributed equally to this manuscript. All authors have contributed significantly to this publication.

Corresponding Author: Eleonora De Luca, UOC di Dermatologia, Università Cattolica del Sacro Cuore, L.go F Vito 1 00135 Roma, Italy.
Phone: +39 (0)6 3015 4227 E-mail: deluca.eleonora94@gmail.com
ABSTRACT

**Introduction:** Data about the long-term effectiveness of brodalumab could be valuable in assessing patient adherence to treatment and improving psoriasis management.

**Objective:** The aim of our study was to evaluate the drug survival of brodalumab and identify any predictive factors for discontinuation.

**Methods:** A multicenter retrospective study was conducted in patients with moderate-to-severe psoriasis who were treated for up to 3 years. We extracted data from patient files, related to the characteristics of the patients and the disease. Drug survival analysis was descriptively analyzed using Kaplan–Meier survival curves. Univariable and multivariable analyses were performed to assess baseline patient characteristics that predicted clinical response.

**Results:** The study included 90 patients. Among them, 28 (31.1%) suspended brodalumab through the observation period. At weeks 52, 104 and 156 the median PASI score were 0.0 [0.0 – 0.8], 0.0 [0.0 – 1.0] and 0.0 [0.0 – 0.0], respectively. The estimated cumulative survival rates at weeks 52 and 104 were 86.32% and 78.09%, respectively. In the multivariable survival analysis, predictor factors for overall discontinuation included body mass index (BMI) (OR 1.10, 95% CI 1.03 – 1.18), baseline PASI (OR 1.06, 95% CI 1.02 – 1.10), and psoriatic arthritis (OR 5.05, 95% CI 0.89 - 13.50).

**Conclusions:** Brodalumab has shown long-term effectiveness for up to 3 years. Considering baseline disease severity and patient characteristics could aid in optimizing the long-term management of psoriasis.

Introduction

The management of psoriasis has improved in recent years due to the expansion of available systemic therapies. Biologic drugs target specific immune system pathways involved in psoriasis, allowing for the optimization of clinical responses and the long-term management of patients. The remarkable pharmaceutical improvement in recent years has led to the development of new biologic therapies that target interleukins (IL) 17 and 23, allowing to achieve higher skin clearance with a good safety profile.

Brodalumab is a fully human monoclonal antibody that specifically targets the interleukin-17 receptor A (IL-17RA), inhibiting the signaling pathway of several (IL-17 isoforms involved in psoriasis pathogenesis [1,2]. The rapid action and high efficacy of brodalumab have already been demonstrated in three phase 3 randomized double-blind trials (RCTs): AMAGINE-1, AMAGINE-2, and AMAGINE-3 [3, 4, 5], as well as in real-life settings [6, 7, 8, 9, 10]. For the long-term management of psoriasis, evaluating brodalumab’s drug survival might help to assess its real-world success and patient’s adherence to the treatment, but to date data in literature are scanty.

Herein we present a retrospective real-life multicenter study conducted in a real life Italian cohort, involving patients with moderate to severe psoriasis who were treated with brodalumab for a period up to 3 years.

Method

We conducted a multicenter, retrospective, observational study in patients with psoriasis who started brodalumab therapy between May 2019 and January 2021. We included patients of age >18 years from the following dermatology units in Italy: ‘Tor Vergata’ University of Rome, Catholic University of the Sacred Heart in Rome IRCCS, ‘Daniele Innocenzi’ of University of Rome ‘La Sapienza,’ Polo Pontino and Istituto Dermopatico dell’Immacolata – IRCCS, Rome.

Exclusion criteria were generalized, palmoplantar pustular psoriasis, use of additional systemic therapies for psoriasis, and participation in clinical trials. Patients were treated with brodalumab at the European Medicines Agency (EMA)-approved dosage.

We collected data related to the characteristics of the patients (age, sex, body mass index [BMI], comorbidities, smoking habits) and of the disease (age at onset, previous therapies, and special-site involvement). The severity of psoriasis was measured with the Psoriasis Area and Severity Index (PASI) score at baseline and after 4, 12, 24, 52, 104, and 156 weeks of treatment. Patients obtaining a PASI 90 improvement at week 4 were defined fast responders. Reasons for withdrawal of brodalumab and any adverse event that occurred during treatment were recorded. Discontinuation of therapy was defined as interruption of brodalumab administration for more than 90 days.

Descriptive statistics for continuous variables were reported as medians/means and interquartile ranges (IR)/standard deviations (SD), dichotomous variables were described using absolute and relative (%) frequencies. The drug survival analysis was descriptively analyzed using Kaplan–Meier survival curves. Three “events” for drug survival were defined and analyzed separately. (i.e. overall discontinuation; discontinuation because of brodalumab ineffectiveness; adverse events or other type of events other than ineffectiveness).
Patients were censored when lost to follow-up, discontinued due to an event other than the events of interest, or when the database was extracted, and patients were actively undergoing their treatment with the drug of interest at that moment. Univariable and multivariable Cox regression analyses were carried out using variables considered of clinical importance. Statistical significance was set at p-value <0.05. Analyses were performed in May 2023 by using STATA 13.0 Software (StataCorp, Texas).

The protocol was reviewed and approved by Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Prot N.: 15188/23. All patients signed a hospital-based informed consent. The study was performed following the principles of the Declaration of Helsinki.

**Results**

Ninety patients with moderate- to- severe plaque psoriasis treated with brodalumab were included. Mean age of patients was 52.2 (SD 15.0) years, and the majority (67.8%) were males. Median PASI score at baseline was 15.0 (IR 10.0 - 22.0). Other baseline characteristics of patients are presented in Table 1. Data about the first 52 weeks of treatment have been already reported [11]. In particular, 29/90 (32.2%) patients achieved PASI 90 at week 4 and were considered fast responders.

Among 90 enrolled patients, 28 (31.1%) suspended brodalumab through the observation period. At weeks 52, 104, and 156 the median PASI score were 0.0 [0.0 – 0.8], 0.0 [0.0 – 1.0] and 0.0 [0.0 – 0.0], respectively. The reasons for discontinuation were adverse events in 8 patients (8.9%), ineffectiveness in 15 patients (16.7%) and loss to follow-up in 5 patient (5.6%). Discontinuation for adverse events were due to eczematous eruptions in 2 patients, and in singular cases to recurrent candidiasis, lower limb myalgia, myocardial infarction, cerebral ischemia, concomitant anemia and transaminase increase due to alcohol abuse, and to recurrent upper respiratory tract infection. Median time of observation among those who discontinued brodalumab was 62.5 (IR 32.0 – 111.0) weeks after the start of the drug.

The overall drug survival is reported in Figure 1A. Overall, a total of 86.32%, 78.09% of patients was under treatment at weeks 52 and 104 respectively. The drug survival rate for discontinuation due to adverse events was 93.69% (confidence interval [CI] 85.35-97.35), and 92.04% (CI 82.93-96.39) after 52 and 104 weeks, respectively (Figure 1B). The drug survival rate for discontinuation due to ineffectiveness was 93.44% (IC 84.81-97.24) and 87.94% (IC 76.95-93.90) after 52 and 104 weeks, respectively (Figure 1C). Data about 156 weeks were not reported because only 24 patients reached this timepoint.

**Table 1. Clinical and Demographic Characteristics of the Study Population.**

<table>
<thead>
<tr>
<th>Demographic or Clinical Characteristic (total n = 90)</th>
<th>N (%)</th>
<th>Mean (SD), Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>29 (32.22)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>61 (67.78)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52.22 (15.03)</td>
<td></td>
</tr>
<tr>
<td>Age of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29.45 (15.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritic Psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (23.33)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>69 (76.67)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.73 [24.10 – 29.41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44 (48.89)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46 (51.11)</td>
<td></td>
</tr>
<tr>
<td>Nail psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (25.65)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67 (74.44)</td>
<td></td>
</tr>
<tr>
<td>Palmoplantar psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (13.33)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78 (86.67)</td>
<td></td>
</tr>
<tr>
<td>Genital psoriasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (27.78)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65 (72.22)</td>
<td></td>
</tr>
<tr>
<td>Previous Biological Treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (52.22)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43 (47.78)</td>
<td></td>
</tr>
<tr>
<td>Other anti IL17 use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (21.11)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>71 (78.89)</td>
<td></td>
</tr>
<tr>
<td>PASI at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.0 [10.0 – 22.0]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI week 12 (n=90)</td>
<td>0.0 [0.0 – 2.0]</td>
<td></td>
</tr>
<tr>
<td>PASI week 52 (n=85)</td>
<td>0.0 [0.0 – 0.8]</td>
<td></td>
</tr>
<tr>
<td>PASI week 104 (n=73)</td>
<td>0.0 [0.0 – 1.0]</td>
<td></td>
</tr>
<tr>
<td>PASI week 156 (n=24)</td>
<td>0.0 [0.0 – 0.0]</td>
<td></td>
</tr>
<tr>
<td>Fast Responder*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61 (67.78)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (32.22)</td>
<td></td>
</tr>
</tbody>
</table>

*Patients achieving PASI 90 at week 4.
BMI = body mass index; IQR = interquartile range; PASI = Psoriasis Area and Severity Index; SD = standard deviation.

An univariable logistic regression was performed and results are reported in Table 2. In detail, predictive factors for overall drug discontinuation were psoriatic arthritis OR 2.93 (95% CI, 1.30 – 6.61), BMI with an OR of 1.07 (95% CI, 1.02 – 1.13) and baseline PASI OR 1.05 (95% CI, 1.02 – 1.09),
Detailed Report of Cases of Special Interest

Patient #1: Patient with multi-drug resistance, comorbidities, and BMI ≥40. We present the case of a 56-year-old male, with class III obesity, arterial hypertension, hyperuricemia, type II diabetes, hypercholesterolemia and a history of psoriasis from the age of 32. He was in therapy from 2001 to 2002 with cyclosporine discontinued for inefficacy. Then, for more than 10 years he was treated only with topical treatments. In June 2016, ustekinumab was administered (PASI score=42), and then discontinued after 90 weeks for persistence of psoriasis (residual PASI=15). In May 2018, therapy with secukinumab was started, with a lack of response, and therefore switched to guselkumab after 42 weeks of treatment (March 2019, PASI score=15). Even with this last therapy, no improvement was observed after 108 weeks (PASI score=15). Finally, in April 2021, brodalumab treatment was started (Figure 2A), with a rapid improvement after 6 weeks (PASI score= 6, Figure 2B) and a complete remission after 12 weeks. Currently, the patient has reached the second year of treatment with brodalumab, maintaining a complete remission of the disease (Figure 2C).

Patient #2: A complex oncological history and multiple treatment suspensions without recurrences. A 48-year-old woman was affected by moderate-severe psoriasis for nearly 30 years and had undergone various therapies over time, including topical treatments, cyclosporine, and NB-UVB phototherapy, with partial benefit. Two years earlier the patient underwent a conization procedure for cervical intraepithelial neoplasia III (CIN III). However, she was in general good health. At the time of our observation, in December 2019, the patient presented a PASI score of 13 and DLQI of 12 (Figure 3A). She was prescribed brodalumab, which led to a complete remission of psoriasis (PASI 0) and pruritus after 4 weeks, along with a significant improvement in her quality of life (DLQI 4).

After 9 months of therapy, the patient was diagnosed with a right fronto-temporal meningioma. Consequently, she discontinued brodalumab and underwent neurosurgery to remove the tumor. Despite discontinuing the biological therapy, the patient did not experience a relapse of psoriasis until 3 months after the neurosurgical intervention, when she had a recurrence localized to the scalp (Figure 3B). Subsequently, the patient resumed brodalumab after consultation with the neurosurgeon, achieving again the remission of her psoriasis.

Two years later, the patient received a diagnosis of left ovarian fibrothecoma and underwent bilateral ovariectomy and adnexectomy. Additionally, due to the detection of breast calcifications, multiple biopsies were performed, leading to a diagnosis of atypical ductal hyperplasia. As a result, the patient must undergo regular clinical and instrumental follow-ups. During these assessments and surgical

At the multivariable survival analysis (Table 3), positive predictor factors for overall discontinuation resulted BMI OR 1.10 (1.03 – 1.18), baseline PASI OR 1.06 (95% CI, 1.02 – 1.10) and psoriatic arthritis OR 5.05 (95% CI,.89 – 13.50). Factors associated with suspension for ineffectiveness were BMI OR 1.11 (95% CI, 1.01 – 1.23), baseline PASI OR 1.07 (95%CI, 1.02 – 1.13) and psoriatic arthritis OR 11.65 (95% CI, 2.92 – 46.46). No significant predictive factors emerged for discontinuation for adverse events.
### Table 2. Univariable Drug Survival Analysis.

<table>
<thead>
<tr>
<th></th>
<th>Overall (OR (95% CI))</th>
<th>Ineffectiveness (OR (95% CI))</th>
<th>Adverse Events (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.43 (0.60 – 3.44)</td>
<td>1.15 (0.39 – 3.37)</td>
<td>1.59 (0.32 – 7.89)</td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1.00 (0.97 – 1.03)</td>
<td>1.01 (0.97 – 1.04)</td>
<td>0.99 (0.94 – 1.04)</td>
</tr>
<tr>
<td><strong>Arthritic psoriasis</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.93 (1.30 – 6.61)</td>
<td>5.60 (1.94 – 16.17)</td>
<td>1.29 (0.26 – 6.40)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>1.07 (1.02 – 1.13)</td>
<td>1.07 (0.99 – 1.14)</td>
<td>1.09 (1.00 – 1.18)</td>
</tr>
<tr>
<td><strong>Scalp psoriasis</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>3.27 (1.36 – 7.86)</td>
<td>1.96 (0.70 – 5.53)</td>
<td>8.56 (1.05 – 69.76)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Nail psoriasis</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.38 (0.95 – 5.96)</td>
<td>2.63 (0.78 – 8.80)</td>
<td>3.00 (0.67 – 13.57)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Palmoplantar psoriasis</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>0.40 (0.06 – 2.96)</td>
<td>0.75 (0.10 – 5.76)</td>
<td>n.c.</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Genital psoriasis</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.13 (0.95 – 4.81)</td>
<td>1.21 (0.38 – 3.87)</td>
<td>4.94 (1.75 – 20.75)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Previous biological drug</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.47 (0.65 – 3.30)</td>
<td>1.95 (0.65 – 5.83)</td>
<td>1.66 (0.40 – 6.98)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Fast Responder</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.57 (0.71 – 3.48)</td>
<td>1.78 (0.61 – 4.73)</td>
<td>1.24 (0.30 – 5.21)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

| PASI at baseline     | 1.05 (1.02 – 1.09) | 1.05 (1.00 – 1.10) | 1.06 (0.99 – 1.11) | 0.053 |

BMI = body mass index; CI = confidence interval; OR = odds ratio; n.c., non computable; PASI = Psoriasis Area and Severity Index.

### Table 3. Multivariable Survival Analysis.

<table>
<thead>
<tr>
<th></th>
<th>Overall (OR (95% CI))</th>
<th>Ineffectiveness (OR (95% CI))</th>
<th>Adverse events (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.70 (0.26 – 1.85)</td>
<td>0.466</td>
<td>0.46 (0.13 – 1.66)</td>
</tr>
<tr>
<td>Female</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.99 (0.95 – 1.02)</td>
<td>0.99 (0.94 – 1.03)</td>
<td>0.98 (0.93 – 1.04)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>1.10 (1.03 – 1.18)</td>
<td>1.11 (1.01 – 1.23)</td>
<td>1.09 (0.98 – 1.20)</td>
</tr>
<tr>
<td><strong>Baseline PASI</strong></td>
<td>1.06 (1.02 – 1.10)</td>
<td>1.07 (1.02 – 1.13)</td>
<td>1.06 (1.00 – 1.12)</td>
</tr>
<tr>
<td><strong>Arthritic Psoriasis</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>5.05 (1.89 – 13.50)</td>
<td>11.65 (2.92 – 46.46)</td>
<td>1.71 (0.29 – 10.08)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Previous biological drug</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>0.88 (0.34 – 2.23)</td>
<td>0.87 (0.25 – 3.04)</td>
<td>1.67 (0.31 – 8.94)</td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td><strong>Fast Responder</strong></td>
<td>No</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>1.63 (0.71 – 3.74)</td>
<td>1.94 (0.65 – 5.78)</td>
<td>1.08 (0.23 – 5.06)</td>
</tr>
</tbody>
</table>

BMI = body mass index; CI = confidence interval; OR = odds ratio; PASI = Psoriasis Area and Severity Index.
procedures, the patient temporarily discontinued brodalumab therapy without experiencing a recurrence of psoriasis. Upon advice from oncology specialists, she resumed treatment with the maintenance dosage regimen. To date, the patient remains in clinical remission for psoriasis and has not experienced a recurrence of cervical intraepithelial neoplasia or meningioma (Figure 3C).

Patient #3: An obese patient with latent tuberculosis. We present the clinical case of a 52-year-old Caucasian male, a workman and habitual smoker with hypertension, dyslipidemia, and class II obesity (BMI 37.04). The patient had a positive family history of psoriasis and was affected from plaque psoriasis since the age of 16, and psoriatic arthritis for the last 20 years. His clinical presentation was characterized by psoriatic plaques mainly located on the trunk and hands, with a PASI of 36 and a DLQI score of 18 (Figure 4A). Due to the high PASI score and the presence of comorbidities, the patient was screened to start biologic therapy. Infectious examinations revealed a positive result for Quantiferon TB Gold, indicating latent tuberculosis infection. Therefore, isoniazid prophylaxis was initiated, but after only 15 days, it induced an increase in liver enzymes. After an infectious
disease consultation, the tuberculosis prophylaxis was switched to rifampicin. After 30 days of starting tuberculosis prophylaxis and after liver enzyme increase was resolved, the patient began treatment with brodalumab. 12 weeks later, patients achieved complete resolution of psoriasis, including the challenging lesions of the hands (Figure 4B). The patient has currently completed three years of brodalumab treatment, without any recurrence of psoriasis.

**Patient #4: Brodalumab after failure of anti-IL-17 secukinumab.** We present the case of a 38-year-old male patient with an 11-year history of psoriasis. The patient was obese (BMI 34.7), dyslipidemic and smoker (20 cigarettes per day). Previously, he had been unsuccessfully treated with ciclosporin (suspended due to hypertension), etanercept (suspended due to ineffectiveness), and secukinumab (suspended due to lack of efficacy after 2 years). After a partial remission with secukinumab, the patient experienced a recurrence of the disease in November 2019, localized on the legs, trunk, and scalp. Consequently, we decided to initiate brodalumab treatment, considering its rapid action. Remarkably, after only 4 weeks, we observed a near-complete resolution of the disease, with the PASI score decreasing from 10 (at baseline) to 1 (Figure 5). After 3 years, the patient continues to receive brodalumab treatment with complete clearance of psoriasis and no impact on his quality of life (PASI 0; DLQI 0) (Figure 5).

Drug survival is a real-life indicator of treatment success over the long-term, encompassing factors such as drug
efficacy, safety and patient adherence. Considering the diverse range of systemic therapies available for psoriasis, drug survival plays a crucial role in guiding us in the selection of the most suitable treatment option for patients [12].

In this study we assessed the drug survival of brodalumab, a monoclonal antibody targeting the interleukin-17 receptor A (IL-17RA), in patients with moderate to severe psoriasis. The data collected over a 3-year period provided valuable insights into the long-term effectiveness of the drug. In detail, after 52 and 104 weeks, 86.32% and 78.09% of patients, respectively, were still receiving brodalumab. These results demonstrated a favorable drug survival rate, with a significant proportion of patients remaining on the treatment throughout the observation period.

There are currently limited studies available that report the long-term survival rate of brodalumab and they report conflicting data and differences between various anti IL-17 agents [7, 13, 14, 15, 16]. Elgaard et al. reported a low brodalumab survival rate, in detail 65.7% and 57.2% after 1 and 2 years respectively. However, this datum may be explained by the very high percentage of bio-experienced patients (>90%) and by the low number of patients followed up for the whole period of the study. Moreover, Gaudet et al. reported similar results and, in particular, a 1-year survival rate of 70%, analyzing data collected through the brodalumab patient support program in Canada [11, 17]. Our results are in line with the studies by other authors that reported survival rates at 1 year ranging from 85 to 89.9%

Figure 4. Patient #3. (A) At baseline. (B) At week 12.

Figure 5. Patient #4, at baseline and after 4 weeks and 3 years of treatment with brodalumab. The hyperchromic patches can be attributed to post-inflammatory hyperpigmented outcomes.
and at 2 years from 77.32 to 80.0%. In addition, Torres et al. analyzed the drug survival of different IL-17 and IL-23 inhibitors, and brodalumab resulted the IL-17 inhibitor with the highest drug survival at 24 months (overall probability of drug survival of 0.80 compared to 0.79 for ixekizumab, and 0.75 for secukinumab). The higher drug survival of brodalumab compared to other IL-17 inhibitors, although with no statistical significance, appeared also in the recent real-world analysis conducted in the Czech Republic [18, 19].

Finally, Gargiulo et al. recently published an Italian study that involved 606 patients treated with brodalumab, out of which 115 completed a 3-year follow-up. The study confirmed the high persistence in treatment even at 36 months, with a notable survival rate of 85.64% [20].

Discontinuation of brodalumab in our study primarily occurred due to adverse events. The most frequent in our patients was the onset of an eczematous eruption, occurring in 2/90 patients (2.22%). This is a well-known adverse event which can occur during anti IL-17 treatments. Although the exact underlying pathogenetic mechanism is not yet fully understood, it has been hypothesized that the incidence of eczematous eruptions is mainly linked to the overexpression of IL-17 C. Brodalumab, acting on IL-17RA and blocking IL17A, IL-17 F, and IL-17 C, does not result in an increase of IL-17 C and this may explain the lower prevalence of this side effect in our population respect to what is reported for other anti IL17 agents (2.2% vs 5.8%) [21]. Several cases have been described that support this hypothesis. For instance, a patient with an eczematous eruption induced by ixekizumab was treated with brodalumab with success, and a patient with concurrent atopic dermatitis and psoriasis was managed with brodalumab achieving a complete clinical response [22, 23]. Otherwise, brodalumab was well tolerated in our population and only one patient (1/90) experienced another well-known IL17 agent side effect, such as recurrent candidiasis. This is in line with the role of IL-17 in host defense against mucocutaneous candidiasis [24].

Predictive factors associated with suspension due to adverse events in the univariable logistic regression were BMI, scalp psoriasis, and genital psoriasis. It’s now well-established that a higher BMI is associated with increased comorbidities and adverse events, even not directly related to psoriatic therapy, while we do not clinically correlate scalp psoriasis and genital psoriasis with adverse events. These predictive factors were not confirmed in the multivariable analysis.

The optimal safety profile of brodalumab has been also confirmed by its successful use in our reported patients with a complex medical history, such as those with latent tuberculosis and multiple neoplasms (cases 2 and 3, respectively). Moreover, we analyzed predictive factors for drug survival. Psoriatic arthritis and PASI at baseline were identified as positive predictive factors for overall discontinuation and suspension due to ineffectiveness. Psoriatic arthritis affects approximately 30% of patients with psoriasis [25] and therefore the ability of a drug to manage the articular component is important when choosing among the available therapeutic options. Brodalumab showed good results in clinical trials for psoriatic arthritis [26], but evidence in real-world is currently limited [17]. In contrast to our result, in the study of Kojanova et al and of Gkanti et al, psoriatic arthritis resulted associated to a longer drug survival [18, 27].

PASI at baseline can have an impact on the efficacy of treatments for psoriasis [28]. Patients with higher baseline PASI may experience a reduced responsiveness or a loss of efficacy to biological treatments. In fact, although it has not yet been reported in drug survival analyses specific on brodalumab, higher baseline PASI was identified as a predictor of drug discontinuation in the drug survival analysis of IL 17 and IL 23 inhibitors by Torres et al [19]. This finding aligns with our result and confirms that patients with a more severe disease at baseline may have a lower drug survival. Moreover, although two of the reported cases showed a high effectiveness of brodalumab in very obese patients, at the multivariable analysis BMI resulted associated with a mild increase risk (OR 1.10) of discontinuation for all reasons and for ineffectiveness [29]. Although in the post hoc analysis of AMAGINE 2/3 trials BMI was not associated to a lower efficacy of brodalumab [30], in the real-world setting this finding is not always confirmed and obesity in some studies seems to be related to lower efficacy and drug survival [14, 17, 18]. For this reason, a trial is currently ongoing to investigate the administration of a higher dosage of brodalumab in patients with an increased BMI (NCT04306315).

Finally, we did not find significant difference in effectiveness between biologic-naive and bi-experienced patients. This datum is worthy of note since, in the real-world setting, bio-experienced patients represent a therapeutic challenge because they may have developed resistance or ineffectivity to prior biologic treatments. In fact, therapies for psoriasis often have a faster, greater efficacy and longer drug survival in patients who are naive to biologics [31, 32, 33]. The efficacy of brodalumab in bio-experienced patients may be explained with its unique mechanism of action that inhibits the IL17-receptor. This is in line with our cases 1 and 4, pivotal trials and real-world studies showing that brodalumab resulted effective also in patients previously treated with other biologics anti IL-17A. (amagine1-2-3) [34, 35].

Limitations

The limitations of our study are the retrospective study design and the size of the study population. However, the long observation period provide important evidence in a real-world setting.
Conclusions

Brodalumab has shown promising long-term efficacy in the management of moderate to severe plaque psoriasis, in a period up to 3 years. The data presented in our study contribute to the better understanding of brodalumab’s success in real world. Consideration of baseline disease severity, comorbidities, and BMI can help in predicting patient adherence and optimizing the long-term management of moderate to severe plaque psoriasis with brodalumab.

References


20. Gargiulo L, Ibba L, Malagoli P, Argenziano G, Alfano R, Argenziano G. Concurrent Atopic Dermatitis and Pso-
Identifying SCC Lesions Capable of Spontaneous Regression by Using Immunohistochemistry: A Systematic Review and Meta-Analysis

Maryam Hedayati1, Behzad Garousi2, Zahrasadat Rezaei2, Yasaman Nazerian3, Younes Yassaghi3, Arian Tavasol4, Dorsa Bahrami Zanjanbar5, Sanaz Sharifpour6, Amir Golestani7, Mansoor Bolideei8, Farajolah Maleki9

1 Zhejiang University School of Medicine, Hangzhou, China
2 Department of Pathology, Karolinska Institute, Stockholm, Sweden
3 School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4 Student Research Committee, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5 Pharmaceutical Science Research Center, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
6 Islamic Azad University Tehran Medical Branch, Tehran, Iran
7 Students Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
8 The Center for Biomedical Research, Ministry of Education and Ministry of Health, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, China
9 Non-Communicable Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran

Key words: keratoacanthoma (KA), squamous cell carcinoma (SCC), immunohistochemistry, CD10, COX-2, elastic fibers, lesions capable of spontaneous regression


Accepted: November 1, 2023; Published: April 2024

Copyright: ©2024 Hedayati et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. Behzad Garousi, Zahrasadat Rezaei contributed equally to this work.

Corresponding Author: Mansoor Bolideei, The Center for Biomedical Research, Ministry of Education and Ministry of Health, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan 430030, China. E-mail: bolaydaeis@gmail.com

ABSTRACT

Introduction: Keratoacanthoma (KA) and squamous cell carcinoma (SCC) are two cutaneous conditions with morphological resemblance, which can complicate the diagnosis in some cases. Using immunohistochemistry staining of biomarkers could be beneficial in resolving this obstacle.

Objectives: We investigated a variety of biomarkers assessed in different studies in order to find the most important and helpful biomarkers for differentiation between SCC and lesions capable of spontaneous regression.
Methods: MEDLINE via PubMed and Google Scholar database were used to identify relevant literature up to 15 June 2022. The aim of our analyses was to determine the capability of biomarkers to distinguish between SCC and lesions capable of spontaneous regression using calculated individual and pooled odds ratios (OR) and 95% confidence intervals (CI) and I² tests.

Results: Six potential biomarkers were CD10 with pooled OR= 0.006 (95% CI: 0.001–0.057) and I²=0%; COX-2 with pooled OR=0.089 (95% CI: 0.029–0.269) and I²=17.1%; elastic fibers with pooled OR= 6.69 (95% CI: 2.928–15.281) and I²=0%; IMP-3 with pooled OR=0.145 (95% CI: 0.021–1.001) and I²=44.5%; P53 with pooled OR=0.371 (95% CI: 0.188– 0.733) and I²=55.9%; AT1R with OR=0.026 (95% CI: 0.006– 0.107).

Conclusions: We suggest the utilization of the following IHC biomarkers for discrimination between lesions with spontaneous regression such as KA and SCC: CD10, COX-2, and elastic fibers.

Introduction

Cutaneous squamous cell carcinoma is the second most common non-melanoma malignant tumor of the skin, following basal cell carcinoma (BCC), and is also the leading cause of death related to non-melanoma skin cancer. The incidence rate of cutaneous SCC is rising continuously, primarily because of population aging and an increased screening rate [1, 2]. It is characterized by the uncontrolled proliferation of atypical keratinocytes within the epidermis, which should be excised. Apart from population aging, other risk factors are mainly genetic factors, male sex, smoking, immunosuppression, and ultraviolet irradiation, primarily due to sun exposure [3, 4]. Early diagnosis of such lesions is crucial. The diagnosis is based on the appearance, location (sun-exposed), and the patient’s medical history. More importantly, the physician’s suspicion would lead to more evaluation and eventually to reaching the diagnosis [5]. The gold standard for SCC diagnosis is still to obtain a skin biopsy and histopathologic evaluation[6].

Keratoacanthoma (KA), on the other hand, is considered a premalignant lesion with the potential capacity for transformation into SCC and is, therefore, a precursor of SCC. However, meta-analysis studies have pointed out a 12% probability of the transformation of KA into SCC [7]. Indeed, KA is a spontaneously regressing type of SCC [8]. If not transformed into SCC, KA would regress spontaneously within weeks [9]. Similar to SCC, the gold standard method of diagnosis of lesions capable of spontaneous regression is tissue biopsy and histological findings [7].

It should be mentioned that some studies consider KA, which are lesions capable of spontaneous regression, as a sub-branch of SCC [10, 11], and other studies do not consider these two diseases as separate from each other [12]. Although the features of these 2 types of lesions are alike in some aspects, the outcomes diverge. Hence, it is imperative to discriminate between these lesions. Nevertheless, a solid criterion is lacking for this manner [9]. A number of studies have assessed the role of diverse cellular and nuclear markers in the differentiation between these two lesions. Some of these markers have been evaluated in several studies, while other markers have been determined in single studies. In this study, we intended to analyze the effectiveness of these markers in identifying lesions capable of spontaneous regression like KA and SCC.

2. Methods

The present systematic review and meta-analysis was performed based on the PRISMA statement.

2.1 Search Strategy and Screening

To determine research studies that assessed Immunohistochemistry (IHC) biomarkers participating in differentiating between SCC and lesions capable of spontaneous regression, a literature search was conducted using ‘MEDLINE via PubMed and Google Scholar database up to 15 June 2022. The following keywords were used in the search: “keratoacanthomas,” “KA,” “lesions capable of spontaneous regression,” “squamous cell carcinoma,” “SCC,” “differentiation,” “diagnoses,” “biomarkers,” and “IHC.” The authors screened the titles, abstracts, and full texts of selected articles to choose the relevant articles.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria based on the full text were: (1) assessing the IHC biomarkers in differentiating between SCC and lesions capable of spontaneous regression; (2) analyzing the IHC biomarkers on subtypes of skin cancers that must contain lesions capable of spontaneous regression and SCC. The exclusion criteria were: (1) publications not in English; (2) non-IHC methods; (3) analysis of other subtypes of skin cancers without containing both SCC and lesions capable of spontaneous regression.
2.3 Data Extraction
Two authors reviewed all the suitable publications. Extracted data were organized into an Excel spreadsheet. The following data were collected from each study: first author’s name, publication year, journal, biomarker(s), sample size (total and individual SCC and lesions capable of spontaneous regression), IHC staining positivity of lesions capable of spontaneous regression samples, and the significance of statistical analyses (obtained P value).

2.4 Statistical Analysis
R software was used to conduct statistical analyses to compare the odds ratio (OR) with 95% CI of SCC and lesions capable of spontaneous regression. Pooled ORs with 95% CI and I² test for heterogeneity were calculated for the biomarkers investigated in at least 2 publications. The consistency of studies was evaluated by the I² heterogeneity test, which is interpreted as follows: 0% represents no inconsistency, and 100% represents total heterogeneity. The significance of heterogeneity was considered if the P value was <0.1.

3. Results
3.1 Relevant Studies and Flowchart
Among 64 relevant manuscripts, 33 were excluded based on the inclusion and exclusion criteria. Thirty-one relevant publications from 1989 to 2021 were reviewed, and data were extracted for analysis (Table 1). Overall, 43 biomarkers were studied, of which 14/43 were assessed in at least two studies, and 23/43 were investigated once. This selection is shown in Figure 1. The OR and 95% CI of these biomarkers were evaluated. Finally, seven significantly effective biomarkers that could differentiate between SCC and lesions capable of spontaneous regression were selected and are discussed.

3.2 Meta-analysis
The individual and pooled OR and P values of 24 single [13-26] and 13 repeated [14, 18-20, 23-25, 27-41] biomarkers are listed in Table 2 and Table 3. The odds of lesions capable of spontaneous regression IHC staining of a specific biomarker, compared with SCC, represent the OR. Calculated infinite OR was excluded due to insensible analysis. However, in order to include studies with zero calculated OR, Peto's method was used. These selected biomarkers’ capability to differentiate between SCC and lesions capable of spontaneous regression was demonstrated by statistically significant OR with 95% CI. AT1R was the single IHC biomarker, and CD-10, COX-2, elastic fibers, IMP-3, and P53 were repeated IHC biomarkers.

3.3 Cluster of Differentiation 10
The cluster of differentiation (CD) 10 is a cell surface enzyme marker used for the diagnosis and differentiation of cancers [42]. There is a correlation between tumor cell proliferation and the number of CD10+ dermal tumor-associated macrophages (TAM) and epidermal Langerhans cells (LC) in the development of epidermal tumors. Indeed, these components are important cellular elements of the tumor microenvironment. It has been reported that the number of LCs in SCC and malignant melanoma is lower than in normal skin. It is assumed that the induction of CD10+ stromal cells may be associated with the infiltration of TAMs and loss of LCs. Therefore, CD10+ stromal cell induction, increased TAMs, and decreased LCs are related to each other, and these 3 items correlate with the rate of tumor proliferation [27]. Two similar studies were evaluated to determine whether CD-10 can serve as a differentiating biomarker for SCC and lesions capable of spontaneous regression compared to SCC, meaning that the tendency of SCC lesions to have positive IHC staining for CD-10 was 166.7 times higher in comparison with lesions capable of spontaneous regression. There was also no statistically significant heterogeneity between studies (I²=0%).

3.4 Cyclooxygenase 2
Cyclooxygenase 2 (COX2) is a key enzyme that produces prostaglandins involved in the inflammatory process [43]. A total of two studies were reviewed for this biomarker [23, 29]. The pooled OR of these studies (lesions capable of spontaneous regression compared with SCC) was calculated at 0.089 (95% CI: 0.029–0.269). These two studies did not have heterogeneity since I²=17.1%. For this reason, the OR of COX-2 IHC staining for SCC compared with lesions capable of spontaneous regression was 11.2.

3.5 Elastic Fiber
Elastic fibers are extracellular components that exist in many tissues, such as the skin, and are important for the skin’s physiological processes [44]. Data extracted from two studies [30, 45] were assessed for this biomarker, revealing a calculated pooled OR of 6.69 (95% CI: 2.928–15.281) for lesions capable of spontaneous regression compared with SCC. Of 118 total samples, 47 were positive for lesions capable of spontaneous regression, while 15 were positive for SCC. The calculated I² was 0%, meaning that the studies were consistent with one another.
Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total sample size</th>
<th>Mean Age (KA)</th>
<th>Mean Age (SCC)</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urano et al. [33]</td>
<td>1992</td>
<td>27</td>
<td></td>
<td></td>
<td>P53</td>
</tr>
<tr>
<td>Kerschmann et al. [35]</td>
<td>1994</td>
<td>50</td>
<td></td>
<td></td>
<td>P53</td>
</tr>
<tr>
<td>Watanabe et al. [77]</td>
<td>2015</td>
<td>40</td>
<td></td>
<td></td>
<td>P53/Ki-67/CD-34/CD-105</td>
</tr>
<tr>
<td>Cain et al. [36]</td>
<td>1995</td>
<td>24</td>
<td></td>
<td></td>
<td>P53/PCNA</td>
</tr>
<tr>
<td>Sakiz et al. [20]</td>
<td>2009</td>
<td>29</td>
<td></td>
<td></td>
<td>P53/P63</td>
</tr>
<tr>
<td>Batinac et al. [37]</td>
<td>2006</td>
<td>120</td>
<td>68.5</td>
<td>76.3</td>
<td>P53/Ki-67/BAK/Bcl-2/</td>
</tr>
<tr>
<td>Khodaeiani et al. [38]</td>
<td>2013</td>
<td>18</td>
<td></td>
<td></td>
<td>p53/ki-67/</td>
</tr>
<tr>
<td>Bedir et al. [25]</td>
<td>2016</td>
<td>70</td>
<td>71</td>
<td>74</td>
<td>p53/ki-67/p16/p21/p27</td>
</tr>
<tr>
<td>Putti et al. [23]</td>
<td>2004</td>
<td>41</td>
<td></td>
<td></td>
<td>P53/COX-2/Telomerase</td>
</tr>
<tr>
<td>Leblebici et al. [84]</td>
<td>2017</td>
<td>51</td>
<td>63.7</td>
<td>74.6</td>
<td>Ki-67/Cytokeratin-17</td>
</tr>
<tr>
<td>Takahara et al. [27]</td>
<td>2009</td>
<td>30</td>
<td></td>
<td></td>
<td>Ki-67/CD-10/CD-68/CD-1a</td>
</tr>
<tr>
<td>Soddu et al. [32]</td>
<td>2013</td>
<td>67</td>
<td>69.5</td>
<td>76.1</td>
<td>IMP-3</td>
</tr>
<tr>
<td>Kanzaki et al. [31]</td>
<td>2016</td>
<td>23</td>
<td>61.7</td>
<td>78.4</td>
<td>IMP3</td>
</tr>
<tr>
<td>Hua et al. [29]</td>
<td>2015</td>
<td>55</td>
<td></td>
<td></td>
<td>COX-2</td>
</tr>
<tr>
<td>Markey et al. [19]</td>
<td>1990</td>
<td>15</td>
<td></td>
<td></td>
<td>B2M/MHC II</td>
</tr>
<tr>
<td>Graham et al. [39]</td>
<td>1987</td>
<td>91</td>
<td>62.4</td>
<td>69.7</td>
<td>B2M</td>
</tr>
<tr>
<td>Jordan et al. [45]</td>
<td>1991</td>
<td>100</td>
<td>66.2</td>
<td>74</td>
<td>Elastic Fiber</td>
</tr>
<tr>
<td>Kaabipour et al. [40]</td>
<td>2006</td>
<td>48</td>
<td>66.3</td>
<td>74.5</td>
<td>P16</td>
</tr>
<tr>
<td>Tan et al. [26]</td>
<td>2009</td>
<td>55</td>
<td></td>
<td></td>
<td>Bcl-x</td>
</tr>
<tr>
<td>Tanikawa et al. [41]</td>
<td>1992</td>
<td>12</td>
<td></td>
<td></td>
<td>P21</td>
</tr>
<tr>
<td>Cabibi et al. [17]</td>
<td>2016</td>
<td>30</td>
<td>62</td>
<td>74</td>
<td>HSP60/CD-1a</td>
</tr>
<tr>
<td>Gambichler et al. [22]</td>
<td>2017</td>
<td>47</td>
<td></td>
<td></td>
<td>PD-L1</td>
</tr>
<tr>
<td>Kronic et al. [15]</td>
<td>1998</td>
<td>36</td>
<td></td>
<td></td>
<td>Dsg1 and Dsg2</td>
</tr>
<tr>
<td>Takeda et al. [13]</td>
<td>2001</td>
<td>72</td>
<td></td>
<td></td>
<td>AT1R</td>
</tr>
<tr>
<td>Jia et al. [16]</td>
<td>2021</td>
<td>45</td>
<td>63</td>
<td>63.6</td>
<td>HSP-105</td>
</tr>
<tr>
<td>Tran et al. [21]</td>
<td>2000</td>
<td>55</td>
<td></td>
<td></td>
<td>OSM</td>
</tr>
<tr>
<td>Gouda et al. [28]</td>
<td>2014</td>
<td>35</td>
<td></td>
<td></td>
<td>P53/Ki-67/CD10</td>
</tr>
</tbody>
</table>

3.6 Insulin-like Growth Factor 2 mRNA-binding Protein

The insulin-like growth factor 2 (IGF-2) mRNA-binding protein (IMP) is a protein family that binds to IGF-2 mRNA and regulates its transcription [46]. Previous studies evaluating IMP-3 as a biomarker for differentiating between SCC and lesions capable of spontaneous regression were conducted by Soddu et al. and by Kanzaki et al. [31, 32]. In the former study, 9/34 were positive for lesions capable of spontaneous regression compared to 19/33 for SCC. In the latter study, all eight samples of lesions capable of spontaneous regression were negative, while 10/15 of SCC samples were positive for IHC staining of IMP-3. The pooled OR of these two studies was 0.145 (95% CI: 0.021–1.001), which is defined as a 6.9 times greater tendency of SCC lesions for IMP-3-positive staining compared with lesions capable of
Figure 1. Prisma flow diagram illustrating the selection of articles.

Table 2. Results of 13 biomarkers with repeated studies.

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Pooled OR (KA/SCC)</th>
<th>95% CI</th>
<th>I²</th>
<th>P value of pooled OR (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD10</td>
<td>0.006</td>
<td>0.001 – 0.057</td>
<td>0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COX-2</td>
<td>0.089</td>
<td>0.029 – 0.269</td>
<td>17.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elastic Fiber</td>
<td>6.689</td>
<td>2.928 – 15.281</td>
<td>0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P53</td>
<td>0.371</td>
<td>0.188 – 0.733</td>
<td>55.9%</td>
<td>0.004</td>
</tr>
<tr>
<td>IMP-3</td>
<td>0.145</td>
<td>0.021 – 1.001</td>
<td>44.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Ki-67</td>
<td>OR=0.143</td>
<td>0.026 – 0.774</td>
<td>-</td>
<td>0.024</td>
</tr>
<tr>
<td>B2M</td>
<td>18.13</td>
<td>0.251 – 1309.386</td>
<td>77.6%</td>
<td>0.184</td>
</tr>
<tr>
<td>PCNA</td>
<td>2.032</td>
<td>0.902 – 4.579</td>
<td>-</td>
<td>0.087</td>
</tr>
<tr>
<td>P16</td>
<td>1.176</td>
<td>0.483 – 2.866</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P21</td>
<td>OR=1.75</td>
<td>0.512 – 5.978</td>
<td>-</td>
<td>0.372</td>
</tr>
<tr>
<td>BAK</td>
<td>4.90</td>
<td>0.252 – 95.68</td>
<td>59.9%</td>
<td>0.294</td>
</tr>
<tr>
<td>BCL-2</td>
<td>OR=0.689</td>
<td>0.323 – 1.472</td>
<td>-</td>
<td>0.337</td>
</tr>
<tr>
<td>Caspase 3</td>
<td>2.562</td>
<td>0.032 – 206.1</td>
<td>97.1%</td>
<td>0.674</td>
</tr>
</tbody>
</table>

spontaneous regression. Although the calculated I² test was 44.5%, this heterogeneity was not statistically significant.

3.7 P53

P53 is a tumor suppressant transcription factor that, upon activation, causes downstream events that suppress cell cycle and proliferation [47]. For a careful assessment of the capability of P53 for the differentiation of SCC and lesions capable of spontaneous regression, a total of 12 studies were reviewed [14, 18, 20, 23, 25, 33-38, 48]. There were 730 samples (lesions capable of spontaneous regression=354, SCC=376) with a calculated pooled OR (lesions capable of spontaneous regression compared with SCC) of 0.371 (95% CI: 0.188–0.733). The I² percentage of heterogeneity was 55.9%, which was statistically significant. Individual and pooled ORs are shown in Figure 2.

3.8 Angiotensin II Receptor Type 1

Angiotensin II receptor type 1 (AT1R) is one of the two types of angiotensin II receptors, which, after activation, is responsible for the homeostasis of blood pressure and body electrolytes, alongside other effects. Among the other effects of
### Table 3. Results of 24 biomarkers with single study.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>OR (KA/SCC)</th>
<th>95% CI</th>
<th>Obtained P value from studies</th>
<th>Calculated P value of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT1R</td>
<td>0.026</td>
<td>0.006 – 0.107</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD-20</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>CD-3</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>CD-68</td>
<td>0.981</td>
<td>0.309 – 3.109</td>
<td>N/S</td>
<td>0.974</td>
</tr>
<tr>
<td>Cylid</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>Dsg 1 &amp; 2</td>
<td>10.714</td>
<td>0.559 – 205.382</td>
<td>-</td>
<td>0.116</td>
</tr>
<tr>
<td>FLK-1</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>HSP-105</td>
<td>0.733</td>
<td>0.138 – 3.88</td>
<td>-</td>
<td>0.716</td>
</tr>
<tr>
<td>HSP-60</td>
<td>8.81</td>
<td>0.385 – 201.383</td>
<td>&lt;0.05</td>
<td>0.173</td>
</tr>
<tr>
<td>IkBu</td>
<td>0.264</td>
<td>0.014 – 5.078</td>
<td>N/S</td>
<td>0.377</td>
</tr>
<tr>
<td>MHC-II</td>
<td>1.2</td>
<td>0.121 – 11.865</td>
<td>-</td>
<td>0.876</td>
</tr>
<tr>
<td>MIB-1</td>
<td>0.074</td>
<td>0.004 – 1.348</td>
<td>&lt;0.05</td>
<td>0.079</td>
</tr>
<tr>
<td>NF-kB</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>OSM</td>
<td>3.529</td>
<td>0.947 – 13.153</td>
<td>0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>P63</td>
<td>Infinite</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PD-L1</td>
<td>1.357</td>
<td>0.387 – 4.759</td>
<td>-</td>
<td>0.633</td>
</tr>
<tr>
<td>STAT-3</td>
<td>0.49</td>
<td>0.023 – 10.571</td>
<td>N/S</td>
<td>0.649</td>
</tr>
<tr>
<td>Survivin</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>TRAP-1</td>
<td>0.708</td>
<td>0.137 – 3.666</td>
<td>N/S</td>
<td>0.681</td>
</tr>
<tr>
<td>Telomerase</td>
<td>0.448</td>
<td>0.017 – 11.659</td>
<td>0.001</td>
<td>0.629</td>
</tr>
<tr>
<td>nm-23</td>
<td>Infinite</td>
<td>-</td>
<td>0.189</td>
<td>-</td>
</tr>
<tr>
<td>P-27</td>
<td>Infinite</td>
<td>-</td>
<td>0.744</td>
<td>-</td>
</tr>
<tr>
<td>pRb</td>
<td>Infinite</td>
<td>-</td>
<td>N/S</td>
<td>-</td>
</tr>
<tr>
<td>Bcl-xl</td>
<td>1.029</td>
<td>0.29 – 3.642</td>
<td>&lt;0.001</td>
<td>0.965</td>
</tr>
</tbody>
</table>

AT1R activation are cell growth and migration [49]. In the study by Takeda et al. [13], AT1R was evaluated in 72 samples (22 lesions capable of spontaneous regression samples compared with 50 SCC samples): 5/22 samples of lesions capable of spontaneous regression were positive on AT1R IHC staining, while 46/50 SCC samples had the same result (calculated P<0.0001). The calculated OR (lesions capable of spontaneous regression in comparison with SCC) was 0.026 (95% CI: 0.006–0.107), meaning that the SCC lesions were 38.4 times more likely to express AT1R than lesions capable of spontaneous regression.

### 4. Discussion

Mentioned above is that the gold standard for the diagnosis of both SCC and lesions capable of spontaneous regression is biopsy sampling and histopathological evaluation, and that all of the evaluated lesion samples in the studies that we reviewed for IHC staining of various biomarkers had been previously diagnosed for SCC or as lesions capable of spontaneous regression. Therefore, it is worth mentioning that IHC staining of these diverse biomarkers is beneficial where a net diagnosis between these two lesions, with the capability of spontaneous regression, is complex and challenging [9, 50]. More importantly, it should be considered that this diversity in biomarkers indicates that the diagnosis based on one biomarker is insensible. Hence, a combination of these biomarkers should be utilized to differentiate between SCC and lesions capable of spontaneous regression. For this reason, we investigated a variety of biomarkers assessed in different studies to identify the most significant and useful biomarkers for this differentiation. Of all 43 biomarkers, after statistical analyses of the extracted data, six biomarkers had significantly more probability of distinguishing between the two entities. Five out of six biomarkers were assessed in two or more studies, including CD-10, COX-2, elastic fibers, IMP-3, and P53. The other biomarker, AT1R, was evaluated in only one study. Other biomarkers that were investigated repeatedly were Ki-67, B2M, PCNA, P16, P21, BAK, Bcl-2, Caspase-3, and CD-1a. Repeated biomarkers are highly important since they give us information across the studies, and their analysis results are more reliable. For a complete
evaluation, the consistency of these studies was assessed by statistical analysis.

The reviewed studies for CD10 had a similar trend of OR for comparison of SCC and lesions capable of spontaneous regression. Therefore, the results of the statistical significance of this biomarker for differentiation are reliable. CD10 is expressed in the epithelial cells of various tissues and has been widely used in diagnosing different skin cancers, including SCC, BCC, and melanoma [51]. The overexpression of CD10 in skin cancer cells promotes rapid tumor progression and proliferation, leading to a higher grade and a larger tumor size [52-54].

Following the analysis for CD10, the pooled OR was calculated at 0.006 (95% CI: 0.001–0.057) for lesions capable of spontaneous regression compared to SCC. For this reason, CD10 can distinguish between SCC and lesions capable of spontaneous regression, since SCC lesions are 166.7 times more likely to be positive for the IHC of this biomarker. Therefore, SCC lesions are biologically more progressive, with a higher proliferation rate, than lesions capable of spontaneous regression [55]. All reviewed studies had the same OR calculation equal to 0.006. Although the number of studies was limited, the combined total sample size of these studies was acceptable. Furthermore, there was no significant heterogeneity between studies, as $I^2 = 0\%$. Taken together, CD10 can be used as an applicable biomarker to differentiate between these lesions.

Another biomarker is COX-2, which is expressed in skin lesions and through the production of prostaglandins [56]; it is involved in the initiation, invasion, and angiogenesis of tumors and also participates in the suppression of the immune system [57, 58]. UV exposure can induce COX-2 expression, leading to skin malignancies [59, 60]. COX-2 has been demonstrated to be effective in the differentiation between benign and malignant skin lesions [59, 61].

Two studies were reviewed to assess the capability of COX-2 to differentiate between SCC and lesions capable of spontaneous regression. These studies were consistent since the calculated $I^2=17.1\%$ was not significant. Moreover, the trend of OR of these studies was similar. In this study, we demonstrate that COX-2 IHC positivity was 11.2 times more positive for SCC compared to lesions capable of spontaneous regression since the calculated pooled OR was 0.089 (95% CI: 0.029–0.269). According to these results, we can conclude that SCC has a more progressive and invasive behavior compared to lesions capable of spontaneous regression. Taken together, with a considerable sample size, we can indicate COX-2 as an acceptable biomarker for the differentiation between SCC and lesions capable of spontaneous regression.
Elastic fibers are components of dermal connective tissue that maintain the elasticity of the skin. They have considerable distinguishing capabilities between malignancies. Loss of these fibers more often occurs in malignant tumors than in benign lesions [62-64]. The calculated pooled OR, comparing lesions capable of spontaneous regression with SCC, was 6.69 (95% CI: 2.928–5.281) with I²=0%. Considering the total sample size of these studies, which was 118, and no significant heterogeneity, the results are reliable. The tendency of OR for these two studies was consistent (6.167 and 13.333), confirming the reliability of the results.

The other biomarker is IMP-3. The members of the IMP family are IMP-1, IMP-2, and IMP-3, which bind to the transcript of IGF-2 mRNA [65]. Particularly, the overexpression of IMP-3 has been detected in several malignant cancers [63-70]. Also, the role of this protein has been investigated as a biomarker to differentiate between benign and malignant lesions, including melanoma [71] and SCC [72]. Furthermore, IMP-3 increases the migration of the malignant cells and leads to the invasiveness of the tumor [73]. For this reason, as it is likely that IMP-3 can differentiate between SCC and lesions capable of spontaneous regression, it was evaluated in this manner.

In our study, two studies were reviewed for the assessment of IMP-3 IHC staining. These studies were not significantly heterogeneous; however, the calculated I² was 44.5%, which is high compared to other biomarkers. Therefore, the results should be considered more cautiously. The pooled OR was 0.145 (95% CI: 0.021–1.001), with individual ORs equal to 0.265 and 0.031. This means that SCC lesions’ biological behavior is more invasive than that of lesions capable of spontaneous regression. Although this pooled OR was considered statistically significant, IMP-3 was 3.9 times more likely to be positive for SCC in the Soddu et al. study [32], while in the Kanzaki et al. study [31], it was 32.2 times more likely to be positive for SCC. This suggests the diversity between the results of these two studies. In other words, IMP-3 should be taken into consideration for the differentiation between SCC and lesions capable of spontaneous regression, but more cautiously and in addition to other biomarkers.

P53 protein is one of the most studied tumor suppressant proteins recognized to date. It is capable of regressing and inhibiting tumors, and the development of many tumors may occur with the mutation of the P53 gene [47]. As discussed in other studies, skin cells with previously mutated P53 genes can develop skin lesions after exposure to the sun [74]. It would seem that P53 is a good biomarker for differentiating between malignant tumors and other lesions, especially in the skin, as other studies have investigated in the past and recently [75, 76].

The highest number of studies in our study were reviewed for this biomarker. Among these 12 studies [14, 18, 20, 23, 25, 28, 35-38, 48, 77, 78], two were excluded due to the calculation of OR since the results were calculated as infinite. Of the remaining ten studies, the trend of OR was towards lesions capable of spontaneous regression, while for other studies, this trend was towards SCC. The calculated OR of that single study was 2.67. Considering the weight of the study (11.93%) compared with other studies, this calculated OR could be ignored. The pooled OR comparing the IHC positivity of lesions capable of spontaneous regression and SCC for P53 was 0.371, and it was statistically significant. In other words, SCC would express P53 3.69 times more than lesions capable of spontaneous regression. The reviewed studies were inconsistent since I²= 55.9%, which was statistically significant. However, this heterogeneity of the studies could be considered moderate. This indicates that P53 could distinguish between SCC and lesions capable of spontaneous regression when used as a biomarker, but care should be taken so that it is not assessed without other biomarkers.

Although the activation of AT1R has homeostatic effects, studies suggest its role and expression in different types of malignancies [79]. Also, a number of studies have investigated its expression on cancerous cells, revealing AT1R’s role in tumor genesis [80]. Consistent with this implication, several treatment approaches were utilized for the management of a number of malignancies, and the results were promising [81, 82]. Moreover, IHC staining of this receptor was evaluated in previous studies for skin lesions, which suggests a high probability of its differentiation capability between skin lesions [83]. AT1R was investigated in one study, by Takeda et al. [13]. SCC significantly expressed AT1R compared with lesions capable of spontaneous regression, with OR (lesions capable of spontaneous regression compared with SCC) of 0.026 (95% CI: 0.006–0.107).

Ki-67, aside from the biomarkers discussed above, had a significant OR in our analyses as well. This biomarker was investigated in six studies [14, 25, 34, 37, 38, 84], five of which were excluded during the analyses due to infinite calculated ORs, which were insensitive. The OR of the remaining study was 0.143, indicating a probability of IHC positivity for Ki-6 comparing lesions capable of spontaneous regression with SCC, which was significant. However, when we assessed the excluded studies, all SCC and lesions capable of spontaneous regression samples for each study were entirely positive. This implies that Ki-67 may not be an acceptable biomarker for the differentiation between SCC and lesions capable of spontaneous regression.

Some of the evaluated biomarkers had a high calculated OR compared with other biomarkers, although they were not statistically significant. These biomarkers were B2M, BAK, Dsg1 &2, HSP60, and MIB-1, and their calculated ORs were 18.1, 4.9, 10.7, 8.81, and 0.074, respectively.
Therefore, these biomarkers could be potentially evaluated in future studies for this purpose.

The limitation of our study may be the high number of investigated biomarkers among the small number of studies for each biomarker. Also, there was heterogeneity in the type of reference standard of the studies we reviewed; because the reference standard of the studies was different from one another, and since the number of our studies was not enough, we could not group the studies that were similar in terms of the standard reference into a subgroup or exclude some of them. Therefore, heterogeneity may be seen in the results that was explained above; for future studies, it is therefore suggested to consider studies that have a similar standard reference (such as hematoxylin). In addition, the range of the marker’s cutoff for positivity or negativity was also the same as above. Of course, it should be mentioned that the cutoff of our studies was almost the same, and there were no statistically significant differences.

5. Conclusion

In summary, the results of our study show that a number of biomarkers, including CD10, COX-2, and elastic fibers, have a high capability of differentiating between SCC lesions and lesions with the capability of spontaneous regression, such as KA, in cases with a difficult diagnosis. IMP-3, P53, and AT1R could also be utilized in this manner; however, more investigation is required. The presence of these biomarkers was investigated through IHC staining and can be used in the clinical approach to SCC and KA lesions.

Acknowledgments: No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article. The authors declare that they have no conflict of interest.

Ethical Approval: This review article is exempt from ethical approval.

References


Photodynamic Therapy for the Treatment of Basal Cell Carcinoma: A Comprehensive Review of Randomized Controlled Trials

Ioannis-Alexios Koumprentziotis¹, Natalia Rompoti¹, Konstantinos Liopyris¹, Electra Nicolaidou¹, Alexander Stratigos¹

¹1st Department of Dermatology and Venereology, Andreas Sygros Hospital, National and Kapodistrian University of Athens, Athens, Greece

Key words: basal cell carcinoma, photodynamic therapy, 5-aminolevulinic acid (ALA), methyl aminolevulinate (MAL), skin cancer

DOI: https://doi.org/10.5826/dpc.1402a105

Accepted: January 12, 2024; Published: April 2024

Copyright: ©2024 Koumprentziotis et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. Ioannis-Alexios Koumprentziotis and Natalia Rompoti have equally contributed as first authors.

Corresponding Author: Ioannis-Alexios Koumprentziotis, I. Dragoumi 5, Athens 16121, Greece, Telephone: +30 6937427051, E-mail: giannhskmpr@gmail.com

ABSTRACT

Introduction: Basal cell carcinoma (BCC) is the most common skin cancer worldwide and has been reported to have a rising incidence in the last years. Multiple therapeutic modalities are approved for the treatment of BCC, making it difficult for physicians to choose the most suitable option for every patient. Photodynamic therapy (PDT) using either 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) as photosensitizing agents is an established treatment option for low-risk BCC.

Objectives: This review aims to summarize the available evidence from randomized clinical trials (RCTs) that utilize either ALA or MAL PDT and compare it with other treatment modalities. The main outcomes related to the effectiveness, adverse events, cosmetic outcomes and pain sensation, along with data from long-term follow-ups will be presented and discussed.

Methods: Thorough literature searches were conducted through the electronic databases ClinicalTrials.gov and Pubmed/MEDLINE from inception up to 28 March 2023. Only studies in English were included. All relevant data were extracted accordingly from the eligible studies.

Results: Eight RCTs included superficial BCC (sBCC) alone, 7 included nodular BCC (nBCC), 2 included both sBCC and nBCC and 1 included BCC of unspecified subtype. Follow-up duration ranged from 3 months to 5 years. Both ALA-PDT and MAL-PDT demonstrated acceptable efficacy, adverse events, cosmetic outcomes and pain sensation while no major differences were observed between them. PDT was less effective than surgery but with better reported cosmetic outcomes.

Conclusions: PDT is a safe and efficacious treatment option for sBCC and to a lesser extent nBCC.
Introduction

Basal cell carcinoma (BCC) is the most common skin cancer worldwide, with an estimated life risk in fair skinned individuals to be around 30%, and along with squamous cell carcinoma (SCC), they account for the vast majority of non-melanoma skin cancers (NMSCs) [1-3]. BCC has been reported to have a rising incidence globally in the last years, while in the US alone more than 2 million people are diagnosed annually, thus increasing healthcare burden and costs [3-6]. Accordingly, data from Canada, Europe, Australia and Asia exhibit rising incidence rates [6-13]. In terms of histopathology and clinical appearance, BCC has a variety of subtypes including nodular, superficial, indurublocystic, fibroepithelial, morpheaform and infiltrative while basosquamous and micronodular mainly exhibit distinct histopathologic features and their presence can alter the prognosis and treatment plan [14-16]. In 2012, Arits et al showed that the proportion of superficial BCC (sBCC) has increased significantly with a decrease of nodular BCC (nBCCs) the last years [17]. Despite that, nBCC still remains the most common subtype with sBCC being the second most common [15,17-19]. Between the different subtypes, nBCC and sBCC are considered to be the least aggressive and with the lowest recurrence rates [18]. While proper identification of each subtype aids in management, a significant number of lesions exhibit more than one histopathologic pattern such as nodular-micronodular which could affect response to therapy [20].

Currently, there are many approved treatment modalities for the treatment of BCC. Surgical excision (SE) and Mohs surgery are considered to be the most efficacious with the highest cure rates among the different treatment options but with noteworthy and unwanted side effects in the treated surfaces like infections and scarring [21-23]. Especially for non-aggressive BCC (sBCC and nBCC) non-surgical interventions can be considered like photodynamic therapy (PDT), 5-fluorouracil (5-FU), imiquimod, radiation, cryotherapy and curettage and electrodesiccation with each presenting varying degrees of effectiveness. Careful patient assessment can guide the physician in order to choose the best possible treatment option for each individual since there are special indications (location of lesion, number of lesions, comorbidities, patient preference and contraindications to surgical intervention) for each treatment modality [22-25]. Data from different guidelines suggest that PDT is a safe and effective choice and should be considered in patients with small (less than 2-cm in diameter), thin (not exceeding 2 mm tumour thickness) sBCCs or nBCCs which are not suitable for surgery or because of patient preference [22-27].

PDT works through the combination of 3 key elements: a photosensitizer, a light source and oxygen. It is performed with topical application of the photosensitizer, which is selectively absorbed by neoplastic cells due to their altered metabolism [28-30]. The most commonly used photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its ester, methyl aminolevulinate (MAL) which are both precursors of the heme biosynthetic pathway. Following the application, ALA is converted into photactivatable porphyrins, specifically protoporphyrin IX (PpIX), in the epidermis and irradiation at pre-defined wavelengths of red, blue or broadband light source causes cytotoxicity mediated by an oxygen-dependent phototoxic reaction and reactive oxygen species (ROS). This process results in the death of the targeted cells through apoptosis, necrosis, or autophagy (Figure 1) [29-32]. A commonly used licensed regimen consists of 2 treatment cycles of PDT, 1 week apart, usually with light curettage of BCCs before the application of the photosensitizer. If the lesions have not fully resolved at the time of the follow-up, re-treatment may be offered [22-27]. PDT is acknowledged as a safe and efficacious option for the treatment of non-aggressive BCC and is utilized in everyday practice. However, since many therapeutic options exist, the decision-making process demands thorough evaluation of the relative effectiveness and safety of the available alternatives.

Objectives

This review aims to summarize and present all the available evidence from randomized controlled trials (RCTs) utilizing either ALA-PDT or MAL-PDT, with an interest in the efficacy, adverse events (AEs), cosmetic outcomes and pain sensation in order to improve clinical decision making. Data from available follow-ups will be presented in order to add to our knowledge of the long-term results of PDT.

Methods

Thorough literature searches were conducted using “photodynamic therapy” AND “basal cell carcinoma” through the electronic databases ClinicalTrials.gov and Pubmed/MEDLINE from inception up to 28 March 2023. The studies that resulted from the search were assessed in order to identify the eligible ones. For inclusion, a study should meet the pre-specified eligibility requirements: the study should be a RCT, one of the studied interventions should be PDT using either MAL or ALA as a photosensitizer and be compared to another type of PDT, different PDT protocol, placebo or other treatment modality and it should be performed on patients with either nBCC or sBCC or both. Studies should be completed with published available results. Only studies in English were included. All relevant data were extracted accordingly from the eligible studies.
Results

Randomized Controlled Trials of sBCC Treated With PDT

Ten RCTs were identified in our literature search reporting data about sBCCs that were treated with either ALA-PDT or MAL-PDT, and are presented in Tables 1 and 2 [33-48]. Two of the studies include both sBCC and nBCC [45,46], one includes sBCC and Bowen disease (BD) [47] and one study with recurrent BCC without specifying the subtype is presented here [49]. For inclusion, histological confirmation of the BCC was required in all studies [33-47,49] except for one which this was not reported [48]. As presented in table 1, for the assessment of response to treatment, clinical evaluation was the main method with histological confirmation to be utilized only in cases of residual or recurrent lesions [33,34,36-42]. Some trials used clinical evaluation alone [43-45, 47] or clinical and histological together [35,46] for the confirmation of treatment response. Follow-up duration ranged from 1.5 months to 5 years post treatment. MAL-PDT was compared to ALA-PDT in 3 studies. Those studies showed high clearance rates and similar tolerability, AEs and cosmetic outcomes in the patients that attended the follow-ups [33-35,45]. Morton et al, who also included nBCC in their study, showed that the recurrence rates were ≤ 10% at 12 months after the last treatment for both arms of the study [45]. Interestingly, data from another study exhibited lower recurrence rates at 5 years of follow-up after conventional two-stage MAL-PDT compared to fractionated ALA-PDT, although no significant risk of treatment failure was observed in the first 3 years. For both interventions the aesthetic results were rated as good-to-excellent for more than 90% of patients [33,34]. Salimvuory et al compared MAL-PDT, ALA-PDT and hexaminolevulinate (HAL)-PDT and showed no differences in the efficacy and safety between the arms but with a short duration of follow-up at 3 months [35]. SE was compared to 2 sessions, 7 days apart, of MAL-PDT and surgery was statistically more efficacious with better clinical lesion responses at 3 and 12 months. On the other hand, cosmetic outcome, which was assessed by both the investigators and the patients, was significantly better in the MAL-PDT arm. The number of treatment-related AEs was higher in the MAL-PDT arm and those included mostly photosensitivity reactions such as erythema, burning sensation and discomfort. All of the AEs reported were of mild or moderate severity and were well tolerated [41]. Except for PDT, topical treatments like imiquimod and 5-FU are considered to be safe and effective alternatives for sBCC for selected patients [22,23]. The 5-year follow-up results from a RCT indicated the superiority of imiquimod, in
Table 1. Randomized controlled trials of superficial basal cell carcinoma treated with photodynamic therapy

<table>
<thead>
<tr>
<th>First Author</th>
<th>Clinical Trial Identifier</th>
<th>BCC Subtype</th>
<th>Method of initial diagnosis and confirmation of CR</th>
<th>PDT Type</th>
<th>Comparator</th>
<th>PDT-N (Lesions-N)</th>
<th>Comparator-N (Lesions-N)</th>
<th>Follow Up (Months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kessels 2017 [33] Van Delft 2022 [34]</td>
<td>NCT01491711</td>
<td>sBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinically (only in the event of clinical suspicion of residual tumour at 3 months or recurrent tumour at 12 months, a biopsy was performed for histological examination)</td>
<td>MAL-PDT</td>
<td>ALA-PDT</td>
<td>80</td>
<td>82</td>
<td>3m, 12m, 60m</td>
<td>MAL: 95% 75/79 CR (3m) ALA: 96% 76/79 CR (3m) MAL: 89% 65/74 CR (12m) ALA: 96% 72/75 CR (12m) MAL: 91% 48/53 CR (60m) ALA: 76% 44/58 CR (60m)</td>
</tr>
<tr>
<td>Salmivuori 2020 (1) [35]</td>
<td>NCT02367547 EudraCT number: 2014-002746-50</td>
<td>sBCC</td>
<td>Diagnosis: Clinical, dermatoscopic and histological CR confirmation: Histological</td>
<td>MAL-PDT</td>
<td>HAL-PDT</td>
<td>27 (31)</td>
<td>24 (31)</td>
<td>3m</td>
<td>MAL: 97% 30/31 sBCCs CR (3m) HAL: 94% 29/31 sBCCs CR (3m)</td>
</tr>
<tr>
<td>Salmivuori 2020 (2) [35]</td>
<td>NCT02367547 EudraCT number: 2014-002746-50</td>
<td>sBCC</td>
<td>Diagnosis: Clinical, dermatoscopy and histological CR confirmation: Histological</td>
<td>MAL-PDT</td>
<td>ALA-PDT</td>
<td>27 (31)</td>
<td>26 (33)</td>
<td>3m</td>
<td>MAL: 97% 30/31 sBCCs CR (3m) ALA: 91% 30/33 sBCCs CR (3m)</td>
</tr>
<tr>
<td>Arits 2013 (1) [36] Roozeboom 2014 (1) [37] Roozeboom 2016 (1) [38] Jansen 2018 (1) [39, 40]</td>
<td>IS-RCTN79701845</td>
<td>sBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical (In case there was clinical suspicion of basal-cell carcinoma recurrence at the follow-up visits, a 3 mm punch biopsy was taken for histological verification)</td>
<td>MAL-PDT</td>
<td>Imiquimod</td>
<td>202</td>
<td>198</td>
<td>3m, 12m, 36m, 60m</td>
<td>MAL: 84% 165/196 CR (3m) Imiquimod: 90% 170/189 CR (3m) MAL: 87% 135/156 CR (12m) Imiquimod: 93% 153/165 CR (12m) MAL: 92% 116/126 CR (36m) Imiquimod: 99% 143/145 CR (36m) MAL: 70% 107/153 CR (60m) Imiquimod: 84% 124/148 CR (60m)</td>
</tr>
<tr>
<td>First Author</td>
<td>Clinical Trial Identifier</td>
<td>BCC Subtype</td>
<td>Method of initial diagnosis and confirmation of CR</td>
<td>PDT Type</td>
<td>Comparator</td>
<td>PDT-N (Lesions-N)</td>
<td>Comparator-N (Lesions-N)</td>
<td>Follow Up (Months)</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------</td>
<td>------------</td>
<td>------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Arits 2013 (2) [36]</td>
<td>IS-RCTN79701845</td>
<td>sBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical (In case there was clinical suspicion of basal-cell carcinoma recurrence at the follow-up visits, a 3 mm punch biopsy was taken for histological verification)</td>
<td>MAL-PDT</td>
<td>5-FU</td>
<td>202</td>
<td>201</td>
<td>3m, 12m, 36m, 60m</td>
<td>MAL: 84% 165/196 CR (3m) 5-FU: 88% 174/198 CR (3m) MAL: 87% 135/156 CR (12m) 5-FU: 91% 154/169 CR (12m) MAL: 92% 116/126 CR (36m) 5-FU: 95% 138/146 CR (36m) MAL: 70% 107/153 CR (60m) 5-FU: 80% 125/157 CR (60m)</td>
</tr>
<tr>
<td>Roozeboom 2014 (2) [37]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roozeboom 2016 (2) [38]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jansen 2018 (2) [39, 40]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szeimies 2008 [41]</td>
<td>NA</td>
<td>sBCC</td>
<td>Diagnosis: Clinical and histological CR confirmation: Clinical</td>
<td>MAL-PDT</td>
<td>SE</td>
<td>100 (135)</td>
<td>96 (132)</td>
<td>3m, 12m</td>
<td>MAL: 92% 118/128 sBCCs CR (3m) SE: 99% 117/118 sBCCs CR (3m) MAL: 91% 107/118 sBCCs CR (12m) SE: 100% 117/117 sBCCs CR (12m)</td>
</tr>
<tr>
<td>Nguyen 2018 [42]</td>
<td>NA</td>
<td>sBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical (histology in case of suspicion of a residual or recurrent BCC)</td>
<td>MAL-PDT (3h/4h group)</td>
<td>MAL-PDT (3h/5h group)</td>
<td>11 (11)</td>
<td>10 (10)</td>
<td>3m, 12m</td>
<td>MAL (3h/4h): 64% 7/11 CR (3m) MAL (3h/5h): 70% 7/10 CR (3m) MAL (3h/4h): 80% 8/10 CR (12m) MAL (3h/5h): 100% 8/8 CR (12m)</td>
</tr>
<tr>
<td>De Haas 2006 [43]</td>
<td>NA</td>
<td>sBCC</td>
<td>Diagnosis: Clinical and histological CR confirmation: Clinical</td>
<td>ALA-PDT (single illumination 4h)</td>
<td>ALA-PDT (double illumination 4h and 6h)</td>
<td>100 (243)</td>
<td>55 (262)</td>
<td></td>
<td>First year (4 times a year), second year (twice yearly) for up to 5 years. 12m minimum for inclusion ALA single: FU 12m-41m, mean 21m ALA double: FU 12m-32m, mean 17m ALA single: 32/243 recurrent or non-responding lesions (20 were found not to be sBCC) for overall study ALA double: 10/262 recurrent or non-responding lesions (5 were found not to be sBCC) for overall study</td>
</tr>
<tr>
<td>de Vijdler 2012 [44]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1 continues
<table>
<thead>
<tr>
<th>First Author</th>
<th>Clinical Trial Identifier</th>
<th>BCC Subtype</th>
<th>Method of initial diagnosis and confirmation of CR</th>
<th>PDT Type</th>
<th>Comparator</th>
<th>PDT-N (Lesions-N)</th>
<th>Comparator-N (Lesions-N)</th>
<th>Follow Up (Months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morton 2018 [45]</td>
<td>EudraCT number: 2013-003241-42</td>
<td>sBCC, nBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical</td>
<td>MAL-PDT</td>
<td>ALA-PDT</td>
<td>110 (127 sBCCs and nBCCs)</td>
<td>121 (148 sBCCs and nBCCs)</td>
<td>3m, 12m</td>
<td>MAL: 92% 101/110 CR (3m) ALA: 93% 113/121 CR (3m) MAL: 91% 86/94 CR (12m) ALA: 92% 98/107 CR (12m)</td>
</tr>
<tr>
<td>Wang 2001 [46]</td>
<td>NA</td>
<td>sBCC, nBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical and histological</td>
<td>ALA-PDT</td>
<td>Cryotherapy</td>
<td>47 (22 sBCC, 25 nBCC)</td>
<td>41 (17 sBCCs, 24 nBCCs)</td>
<td>12m</td>
<td>ALA: 38% 8/21 sBCCs and 13% 3/23 nBCCs recurred (12m) Cryotherapy: 7% 1/15 sBCCs and 21% 5/24 nBCCs recurred (12m)</td>
</tr>
<tr>
<td>Ibbotson 2022 [47]</td>
<td>NCT02872909</td>
<td>sBCC, BD</td>
<td>Diagnosis: NA CR confirmation: Clinical</td>
<td>MAL-PDT</td>
<td>MAL-PDT (APDT)</td>
<td>18 (8 patients with sBCC)</td>
<td>34 (19 patients with sBCC)</td>
<td>3m, 6m, 12m</td>
<td>Of the APDT group, 77.8% (–6.6%, 95% confidence interval for difference –30% to 16%) were clear at 1 year compared with 84.4% with CPDT (P = 0.56) (data for both sBCC and BD patients)</td>
</tr>
<tr>
<td>Basset-Seguin 2008 [48]</td>
<td>NCT00469417</td>
<td>sBCC</td>
<td>Diagnosis: Histological CR confirmation: NA</td>
<td>MAL-PDT</td>
<td>Cryotherapy</td>
<td>60 (114)</td>
<td>58 (105)</td>
<td>3m, 5y</td>
<td>MAL: 88% 100/114 CR 3m Cryotherapy: 89% 93/105 CR 3m 5-year recurrence rates: 20% with cryotherapy versus 22% with MAL PDT, P = 0.86</td>
</tr>
<tr>
<td>Osiecka 2012 [49]</td>
<td>NA</td>
<td>Recurrent BCC (unknown subtype)</td>
<td>Diagnosis: Histologically CR confirmation: Clinical and photodynamic diagnosis</td>
<td>ALA-PDT + Imiquimod</td>
<td>PDT + Placebo</td>
<td>24</td>
<td>10</td>
<td>1,5m</td>
<td>ALA+imiquimod: 75% 18/24 CR 1.5m Placebo: 60% 6/10 CR 1.5m</td>
</tr>
</tbody>
</table>

ALA = aminolevulinic acid; APDT = ambulatory PDT; BCC = basal cell carcinoma; BD = Bowen disease; CPDT = conventional PDT; CR = complete response; FU = follow-up; sBCC = superficial basal cell carcinoma; HAL = hexaminolevulinate; m = months; MAL = methyl aminolevulinate; NA = not available; nBCC = nodular basal cell carcinoma; SE = surgical excision; 5-FU = 5-Fluourouracil.
Table 2. Adverse events, Cosmetic outcomes and Pain of superficial basal cell carcinoma treated with photodynamic therapy

<table>
<thead>
<tr>
<th>First author</th>
<th>Adverse events</th>
<th>Cosmetic outcomes</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kessels 2017 [33]</td>
<td>• Moderate/severe erythema</td>
<td>• Good-to-excellent</td>
<td>• Pain score, mean NRS ± SD</td>
</tr>
<tr>
<td>Van Delft 2022 [34]</td>
<td>MAL: 28/73, ALA: 59/80</td>
<td>MAL: 48/72 (end of initial evaluation)</td>
<td>PDT1</td>
</tr>
<tr>
<td></td>
<td>swelling MAL: 5/73, ALA: 9/80</td>
<td>ALA: 58/73 (end of initial evaluation)</td>
<td>MAL: 2.25 ± 2.54</td>
</tr>
<tr>
<td></td>
<td>crusts MAL: 6/73, ALA: 15/80</td>
<td>MAL: 56/59 (as judged by patients 5 years after)</td>
<td>ALA: 1.88 ± 2.36</td>
</tr>
<tr>
<td></td>
<td>vesicles MAL: 5/73, ALA: 18/80</td>
<td>ALA: 61/63 (as judged by patients 5 years after)</td>
<td>PDT2</td>
</tr>
<tr>
<td></td>
<td>pruritus MAL: 13/73, ALA: 16/80</td>
<td></td>
<td>MAL: 2.48 ± 2.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ALA: 3.36 ± 2.57</td>
</tr>
<tr>
<td>Salmivuori 2020 [35]</td>
<td>• Moderate-to-severe post treatment reactions</td>
<td>• Good-to-excellent by number of lesions</td>
<td>No differences in pain during illumination (MAL vs BF-200 ALA vs HAL; PDT I 4 min P=0.21, 8 min P=0.18; PDT II 4 min P=0.47, 8 min P=0.87). In the HAL group, the second session was more painful than the first session (PDT I vs PDT II; 4 min P=0.006, 8 min P=0.005). No difference in pain between sessions in the other arms (PDT I vs PDT II; MAL 4 min P=0.17, 8 min p=0.79; BF-200 ALA 4 min P=0.45, 8 min P=0.43).</td>
</tr>
<tr>
<td></td>
<td>MAL: 22/31</td>
<td>MAL: 24/31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HAL: 25/31</td>
<td>HAL: 19/31</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALA: 24/33</td>
<td>ALA: 25/33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 treatment-related withdrawal from the trial, as one patient from the MAL group experienced remarkable swelling, edema, erythema, and hematoma in the treatment area after PDT I.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arits 2013 [36]</td>
<td>• Moderate-to-severe patient reported AEs</td>
<td>• Good-to-excellent at 12 months</td>
<td>• Moderate-to-severe</td>
</tr>
<tr>
<td>Jansen 2018 [39,40]</td>
<td>First week redness</td>
<td>MAL: 116/186 (lesions)</td>
<td>First treatment</td>
</tr>
<tr>
<td></td>
<td>itching MAL: 18/191, Imiquimod: 35/189, 5-FU 20/191</td>
<td></td>
<td>Second week</td>
</tr>
</tbody>
</table>

Table 2 continues
Table 2. Adverse events, Cosmetic outcomes and Pain of superficial basal cell carcinoma treated with photodynamic therapy (continued)

<table>
<thead>
<tr>
<th>First author</th>
<th>Adverse events</th>
<th>Cosmetic outcomes</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szeimies 2008 [41]</td>
<td>• Photosensitivity reaction (all expected reactions such as skin discomfort, burning sensation, erythema, stinging, among others, reported with MAL-PDT) MAL: 31/100, SE: NA wound infection MAL: NA, SE: 5/96 milia MAL: 2/100, SE: NA wound dehiscence MAL: NA, SE: 2/96</td>
<td>• Investigator assessment (12m) MAL: 77/83 success (mean cosmetic outcome across lesions at least good) SE: 44/86 success (mean cosmetic outcome across lesions at least good)</td>
<td>• Pain MAL: 2/100 SE: 1/96 • Post procedural pain: MAL: NA, SE: 3/96</td>
</tr>
<tr>
<td>Myanmar 2018 [42]</td>
<td>NA</td>
<td>NA</td>
<td>• Median VAS score after 1st illumination (range) MAL-PDT (3h/4h group): 3 [0-7.0] MAL-PDT (3h/5h group): 4.5 [2.0-7.0]</td>
</tr>
<tr>
<td>De Haas 2006 [43]</td>
<td>In the 2-fold illumination, crusts formed following therapy in 15 lesions in six patients. In the single illumination group, crusts were seen in two lesions in two patients. One patient showed a pustular skin reaction in 11 of 16 lesions, which lasted 5 days. A small number (19) showed persistent hypopigmentation at the illumination site 1 year after therapy. Cosmetic outcome was good in all lesions.</td>
<td>In the single illumination group, five patients required pain relief for six of 32 treated lesions. In the 2-fold illumination group, 15 patients required pain relief for 44 of 64 treated lesions</td>
<td></td>
</tr>
<tr>
<td>Morton 2018 [45]</td>
<td>MAL: Patients with related TEAEs rated as local skin reaction 130/143 ALA: Patients with related TEAEs rated as local skin reaction 121/138 Most commonly reported TEAEs in both groups were local reactions at the application site (pain, erythema, pruritus, and edema). The majority of related TEAEs were of mild-to-moderate intensity. MAL EOS: 36/74 good or very good, 24/74 satisfactory, 14/74 unsatisfactory or impaired MAL 1yFUP: 39/57 good or very good, 8/57 satisfactory, 10/57 unsatisfactory or impaired ALA EOS: 42/70 good or very good, 16/70 satisfactory, 12/70 unsatisfactory or impaired ALA 1yFUP: 41/56 good or very good, 8/56 satisfactory, 7/56 unsatisfactory or impaired</td>
<td>Maximal pain sensation during PDT (means and (SD)) PDT1 MAL: 3.6 (2.22), ALA: 3.7 (2.42) PDT2 MAL: 4.1 (2.66), ALA: 4.5 (2.69) PDT3 MAL: 2.5 (2.23) ALA: 2.8 (2.55) PDT4 MAL: 2.9 (2.75) ALA: 3.9 (2.97)</td>
<td></td>
</tr>
<tr>
<td>First author</td>
<td>Adverse events</td>
<td>Cosmetic outcomes</td>
<td>Pain</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>------</td>
</tr>
<tr>
<td>Wang 2001</td>
<td>• Time and course of healing. Significantly shorter healing time after ALA-PDT as compared with cryosurgery and was manifested by less edema and leakage, but not erythema, 1 week after treatment. None of the PDT treated lesions was classified as severe concerning leakage, edema and erythema. In the cryosurgery group, four lesions had severe leakage, one severe edema and one severe erythema. At the first follow-up, 12 crusts were necrotic following cryosurgery compared with only six after PDT.</td>
<td>• 1 year assessment ALA: 21/42 excellent, 18/42 good, 1/42 acceptable, 2/42 blemished Cryosurgery: 3/37 excellent, 17/37 good, 7/37 acceptable, 10/37 blemished.</td>
<td>• mean ± SD VAS scores ALA: 43 ± 31 mm Cryosurgery: 32 ± 27 mm A few hours and 7 days after the treatment, the average VAS scores were 3.4 mm and 1.4 mm, respectively, for PDT. The corresponding numbers were 8.3 and 1.8 for cryosurgery.</td>
</tr>
<tr>
<td>Ibbotson 2022</td>
<td>Erythema was slightly greater with APDT (median 2) (CPDT median 1; 95% confidence interval for difference 1 to 0, P = 0.025) (erythema: 0–3; none, mild, moderate, severe) (data for both sBCC and BD patients)</td>
<td>The geometric mean patient satisfaction scores at 1 year (available for 24 APDT, 14 CPDT) were 9.63 and 9.27 for APDT and CPDT, respectively (P = 0.34). (data for both sBCC and BD patients)</td>
<td>The geometric mean VAS pain scores were 1.55 for APDT and 2.62 for CPDT (P = 0.36) (data for both sBCC and BD patients)</td>
</tr>
<tr>
<td>Basset-Seguin</td>
<td>NA</td>
<td>Excellent cosmetic outcome with MAL PDT (60% versus 16% with cryotherapy, P = 0.00078)</td>
<td>NA</td>
</tr>
</tbody>
</table>

ALA = aminolevulinic acid; BD = Bowen disease; EOS = end of clinical study; FUP = follow-up; MAL = methyl aminolevulinate; HAL = hexaminolevulinate; NA = not available; NRS = numeric rating scale; PDT = photodynamic therapy; SD = standard deviation; SE = surgical excision; TEAE = treatment emergent adverse event; VAS = visual analog scale; 1yFUP = 1 year follow-up; 5-FU = 5-Fluorouracil.

terms of effectiveness, when compared to 5-FU and MAL-PDT while no major AEs were reported for any arm [36-40]. Data regarding cosmetic outcome suggest that those 3 non-invasive options are better than retreatment of recurrent BCC with excision or an alternative treatment, with PDT having the best cosmetic results at 5 years in recurrence-free patients [39]. A trial tested a combination of ALA-PDT and imiquimod vs placebo for recurrent unspecified BCC and the results of the combination treatment showed a 75% complete response (CR) at 6 weeks with the remaining lesions significantly reducing in size. Interestingly, in this study photodynamic diagnosis (PDD) was used to detect and visualize suspicious sites (including cancer lesions) that were not detected during routine clinical assessment [49]. NBCCs and sBCCs were treated with ALA-PDT and with cryotherapy in a different RCT [46]. At 12 months, cryotherapy showed to be more effective in the treatment of sBCC with lowest clinical recurrence rates than ALA-PDT, which was not the case in the treatment of nBCC. Retreatments were required more often with PDT, which can more easily be repeated since it proved significantly shorter healing times and better cosmetic outcomes than cryotherapy [46]. Cryotherapy was compared to PDT in another study but this time, the results showed no difference in 5-year recurrence rates with either treatment, and PDT yielded better cosmetic outcomes [48]. Different illumination regimens were tested in two trials [42-44]. One trial compared a single illumination ALA-PDT scheme performed at 4 hours after the application of ALA to a 2-fold illumination ALA-PDT scheme performed at 4 and 6 hours after application. Follow-ups ranged from 12 to 41 months. CR was higher in the 2-fold illumination protocol but with a higher number of patients requiring pain relief during or after illumination. In general, good tolerability and cosmetic outcomes were reported by both arms [43,44]. A 3 and 4-hour illumination scheme after application of MAL was compared to a 3 and 5-hour illumination scheme after...
application in a different study. This study sought to examine the effects of a single day, double illumination protocol since it would be less expensive and more practical. Results seemed to be promising for both groups with CR at 3 months after treatment to be between 64 and 70%. Some of the failures/reurrences were attributed to the presence of a more aggressive BCC subtype, because of sampling errors of the primary punch biopsy and primary clinical assessment. In this study in four punch biopsies (three initial and one post-treatment), other BCC subtypes were detected after additional sectioning [42]. Pain was well tolerated in both groups and no serious AEs were reported. The study main limitation was the small number of participants, which was 11 and 10 respectively, for each group [42]. A novel low-irradiance ambulatory PDT (APDT) was compared to conventional PDT, with both arms using MAL as the photosensitizing agent for the treatment of sBCC and BD. Both interventions showed similar efficacy at 12 months and a good safety profile. There were no significant differences in the pain scores while erythema was slightly greater in the APDT group. Both treatments were well tolerated, but the results refer to the treatment of both sBCC and BD [47].

In the examined studies, dropouts related to the use of either MAL-PDT or ALA-PDT were very low to none, without life threatening AEs and with the deaths that occurred not attributed to the studied interventions after careful examination. Most commonly, for both ALA and MAL, AEs included topical reactions such as vesiculation, crusting, erythema, swelling, pruritus and edema. Pain and discomfort occurred frequently during and after treatment but eventually both were well tolerated with or without the use of analgesic medication (Table 2) [33-49].

Randomized Controlled Trials of nBCC Treated With PDT

Nine RCTs were identified in our literature search reporting data about nBCCs that were treated with either ALA-PDT or MAL-PDT and are presented at Tables 3 and 4 [50-58], with two of those studies which included both nBCC and sBCC already discussed above and presented at Tables 1 and 2 [45,46]. Similar to sBCC trials, for inclusion histological confirmation was required [50-58]. For the assessment of response to treatment (Table 3), clinical evaluation, with histological confirmation to be utilized only in cases of residual or recurrent lesions, was the preferred method [50-54,57]. One study relied to clinical evaluation alone [56] and two studies used both clinical and histological assessment [55, 58]. Follow-ups ranged from 3 months to 5 years. MAL cream was compared to placebo cream in one trial. For inclusion, histological examination of a 2–3-mm punch biopsy was performed. Both clinical and histological confirmations were required for the evaluation of the treatment outcome. After the application of the photosensitizer, illumination followed for both groups. The higher CR rates were observed with MAL-PDT and concurrently with excellent cosmetic outcomes for both treatment arms. As expected, the incidence of treatment-related AEs and pain was higher with MAL-PDT, with most of them being of mild-to-moderate severity and, resolving within one day. The serious AEs reported were considered not to be related to either treatment modality [55]. 3 trials randomized patients to receive either PDT or SE [51-54,56]. In two of them, ALA cream was utilized, and the results exhibited higher recurrence rates in comparison with SE, especially at 5 years after treatment [51,52,56]. No serious AEs were reported and cosmetic outcomes were equally good for both studies [51,56], but with pain scores being higher in one study, during and immediately after treatment with PDT, which at later assessments had resolved completely [56]. SE was compared to MAL-PDT and the long-term results indicated the superiority of SE in lesion response but with a more favorable cosmetic outcome with PDT. However, more patients experienced pain and topical AEs in the PDT group. In addition, skin infection occurred in 3 patients in the surgery group while no patient in the PDT group had a similar AE [53, 4]. In a different study, Choi et al found that Er:YAG ablative fractional laser with MAL-PDT (Er:YAG AFL-PDT) had notably higher clearance rates than conventional MAL-PDT at 12 months. In this study, the reported short-term efficacy of conventional MAL-PDT was significantly lower than the one reported by previous studies. Despite the better efficacy of Er:YAG AFL-PDT, the cosmetic outcomes, pain scores and AEs were similar for both studied groups. All AEs were of mild to moderate severity and mostly self-limiting, with no patient to discontinue the particular study. Crusting was the most common AE in both groups, followed by erythema, burning sensation and post-inflammatory hyperpigmentation [50]. Another study with 238 patients in total, compared Er:YAG laser-MAL-PDT with MAL-PDT and with Er:YAG laser alone. Patients with at least 3 nBCCs were recruited and all interventions were applied at every patient. At 12 months the group of Er:YAG laser-MAL-PDT had only 2 recurrences, while the MAL-PDT group had 8 and the Er:YAG laser had 16 with all treatments having acceptable aesthetic results. Despite its effectiveness, the Er:YAG laser-MAL-PDT combined therapy was described as very complicated and long-lasting by the participants [58]. High-risk nBCCs were treated with ablative fractional laser (AFXL)-MAL-PDT and conventional MAL-PDT. The AFXL-MAL-PDT showed comparable efficacy with conventional MAL-PDT at 12 months follow-up with a histological assessment despite the fact that short-term results were in favor of AFXL-MAL-PDT which exhibited higher CR at 3 months. For both interventions, cosmesis was very satisfying and no serious AEs
<table>
<thead>
<tr>
<th>First author</th>
<th>Clinical trial identifier</th>
<th>BCC subtype</th>
<th>Method of initial diagnosis and confirmation of CR</th>
<th>PDT type</th>
<th>Comparator</th>
<th>PDT-n (lesions-n)</th>
<th>Comparator-n (lesions-n)</th>
<th>Follow up (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi 2016 [50]</td>
<td>NCT02018679</td>
<td>nBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical and dermoscopy (in case of suspicion of recurrence or treatment failure, histological assessment was performed)</td>
<td>MAL-PDT</td>
<td>YAG-AFL-MAL-PDT</td>
<td>19 (21)</td>
<td>20 (21)</td>
<td>3m, 12m</td>
<td>MAL: 50% CR (3m) YAG-AFL-MAL-PDT: 84.2% CR (3m) MAL: 22.2% CR (12m) YAG-AFL-MAL-PDT: 78.9% CR (12m)</td>
</tr>
<tr>
<td>Mosterd 2008 [51] Roozeboom 2013 [52]</td>
<td>NA</td>
<td>nBCC</td>
<td>Diagnosis: Histological CR confirmation: Clinical (in case of suspicion of recurrence or treatment failure, histological assessment was performed)</td>
<td>ALA-PDT</td>
<td>SE</td>
<td>NA (83)</td>
<td>NA (88)</td>
<td>3m, 12m, 36m, 60m</td>
<td>ALA: 2 treatment failures (3m), 11 treatment failures (12m), 21 treatment failures (36m), 23 treatment failures (60m) SE: 2 treatment failures (3m) which remained throughout the study</td>
</tr>
<tr>
<td>Rhodes 2004 [53] Rhodes 2007 [54]</td>
<td>NA</td>
<td>nBCC</td>
<td>Diagnosis: Clinical and histological CR confirmation: Clinical (in case of suspicion of recurrence or treatment failure, histological assessment was performed)</td>
<td>MAL-PDT</td>
<td>SE</td>
<td>53 (60)</td>
<td>50 (58)</td>
<td>3m, 12m, 24m, 60m</td>
<td>MAL: 91% 48/53 nBCCs CR (3m) SE: 98% 51/52 nBCCs CR (3m) MAL: 83% 44/53 nBCCs CR (12m) SE: 96% 50/52 nBCCs CR (12m) MAL: 76% 32/42 nBCCs CR (24m) SE: 96% 44/46 nBCCs CR (24m) At 5 years (60m) after last treatment, the sustained lesion complete response rate, estimated by the complementary log-log model, was 76% (95% CI, 59%-87%) for MAL-PDT compared with 96% (95% CI, 84%-99%) for SE in the PP population (P = 0.01).</td>
</tr>
<tr>
<td>First author</td>
<td>BCC subtype</td>
<td>Method of initial diagnosis and confirmation of CR</td>
<td>Comparator</td>
<td>PDT type</td>
<td>Follow up (months)</td>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foley 2009</td>
<td>nBCC</td>
<td>Histological</td>
<td>MAL-PDT</td>
<td>66 (75)</td>
<td>3m, 6m</td>
<td>MAL: 75% 5/75 nBCC CR for overall study, Placebo: 27% 20/75 nBCC CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berroeta 2007</td>
<td>nBCC</td>
<td>Histological</td>
<td>MAL-PDT</td>
<td>65 (75)</td>
<td>3m, 6m, 12m</td>
<td>MAL: 88% 14/16 clinical CR 3m, Placebo: 56% 9/16 clinical CR 3m, AFXL: 63% 10/16 histological CR 12m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haak 2015</td>
<td>nBCC</td>
<td>Clinical</td>
<td>MAL-PDT</td>
<td>65 (75)</td>
<td>3m, 6m, 12m</td>
<td>MAL: 56% 9/16 histological CR 12m, AFXL: 63% 10/16 histological CR 12m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smuder 2008</td>
<td>nBCC</td>
<td>Clinical and histological</td>
<td>MAL-PDT</td>
<td>65 (75)</td>
<td>3m, 6m, 12m</td>
<td>MAL: 99% 3/3 CR 3m, Er:YAG-MAL: 99% 3/3 CR 3m, Er:YAG: 92% 3/3 CR 12m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smuder 2008 (2)</td>
<td>nBCC</td>
<td>Clinical and histological</td>
<td>MAL-PDT</td>
<td>65 (75)</td>
<td>3m, 6m, 12m</td>
<td>MAL: 99% 3/3 CR 3m, Er:YAG-MAL: 99% 3/3 CR 3m, Er:YAG: 92% 3/3 CR 12m</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** Randomized controlled trials of nodular basal cell carcinoma treated with photodynamic therapy (continued)

AFL = ablative fractional laser; AFXL = Ablative fractional laser; ALA = aminolevulinic acid; BCC = basal cell carcinoma; CI = confidence interval; CR = complete response; m = months; MAL = methylaminolevulinate; NA = not available; nBCC = nodular basal cell carcinoma; PP = per-protocol; PDT = photodynamic therapy; SE = surgical excision.
### Table 4. Adverse events, Cosmetic outcomes and Pain of nodular basal cell carcinoma treated with photodynamic therapy

<table>
<thead>
<tr>
<th>First author</th>
<th>Adverse events</th>
<th>Cosmetic outcomes</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choi 2016</strong> [50]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>crust</td>
<td>YAG-AFL-MAL-PDT: 17/18, MAL-PDT: 14/16</td>
<td>• Combined excellent/good cosmetic outcome rates at 12 months MAL-PDT: 100%, YAG-AFL-MAL-PDT: 93.8%</td>
</tr>
<tr>
<td></td>
<td>erythema</td>
<td>YAG-AFL-MAL-PDT: 17/18, MAL-PDT: 14/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>burning sensation</td>
<td>YAG-AFL-MAL-PDT: 15/18, MAL-PDT 12/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hyperpigmentation</td>
<td>YAG-AFL-MAL-PDT: 12/18, MAL-PDT: 9/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>itching</td>
<td>YAG-AFL-MAL-PDT: 4/18, MAL-PDT: 3/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>scale</td>
<td>YAG-AFL-MAL-PDT: 3/18, MAL-PDT: 2/18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bullae</td>
<td>YAG-AFL-MAL-PDT: 3/18, MAL-PDT 2/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>oozing</td>
<td>YAG-AFL-MAL-PDT: 2/18, MAL-PDT 1/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
<td>YAG-AFL-MAL-PDT: 2/18, MAL-PDT 1/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Combined excellent/good cosmetic outcome rates at 12 months MAL-PDT: 100%, YAG-AFL-MAL-PDT: 93.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rhodes 2007</strong> [54]</td>
<td>skin infection</td>
<td>MAL: 0/52, SE: 3/49</td>
<td>• Skin pain MAL: 7/52, SE: 3/49 (1 patient discontinued due to severe burning sensation which resolved without medical intervention)</td>
</tr>
<tr>
<td></td>
<td>crusting</td>
<td>MAL: 2/52, SE: 0/49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>itching</td>
<td>MAL: 2/52, SE: 0/49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stinging of skin</td>
<td>MAL: 10/66, Placebo: 5/65</td>
<td>• Burning sensation of skin MAL: 19/66, Placebo: 8/65</td>
</tr>
<tr>
<td></td>
<td>crusting</td>
<td>MAL: 5/66, Placebo: 3/65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bleeding skin</td>
<td>MAL: 4/65, Placebo: NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Investigator rated excellent or good cosmetic outcome MAL: 36/44 (3m) SE: 15/45 (3m) MAL: 33/42 (12m) SE: 17/45 (12m) MAL: 24/29 (24m) SE: 16/39 (24m) MAL: 27/31 (60m) SE: 19/35 (60m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Patient rated excellent or good cosmetic outcome MAL: 39/41 (3m) SE: 37/44 (3m) MAL: 41/42 (12m) SE: 36/43 (12m) MAL: 28/29 (24m) SE: 27/36 (24m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Skin pain MAL: 12/66, Placebo: 3/65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Burning sensation of skin MAL: 19/66, Placebo: 8/65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 4 continues*
Table 4. Adverse events, Cosmetic outcomes and Pain of nodular basal cell carcinoma treated with photodynamic therapy (continued)

<table>
<thead>
<tr>
<th>First author</th>
<th>Adverse events</th>
<th>Cosmetic outcomes</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berroeta 2007 [56]</td>
<td>NA</td>
<td>• Mean scar severity following treatment assessed by male assessor ALA: 1.94, SE: 2.07 • Mean scar severity following treatment assessed by female assessor ALA: 2.23, SE: 2.53 (no detectable difference in cosmesis between the two groups)</td>
<td>• During treatment (median) ALA: 5/10, SE: 0/10 • Immediately after treatment (median) ALA: 5/10, SE: 0/10 • At later assessments, with a median pain of 0/10 for both treatments</td>
</tr>
<tr>
<td>Haak 2015 [57]</td>
<td>AEs were predominantly mild with mild scarring being the most frequently observed reaction at 3 months. AEs in terms of scarring pigmented changes were observed to similar extents after AFXL-PDT and PDT at 3, 6, 9 and 12 months.</td>
<td>Good-to-excellent cosmetic outcome rated by physicians at 3 months MAL: 13/14 AFXL: 15/16 Good-to-excellent cosmetic outcome rated by patients at 3 months MAL: 14/14 AFXL: 15/16</td>
<td>• First treatment AFXL-PDT median 3 (IQR 2–55) versus PDT 35 (25–5) • Second treatment AFXL-PDT 35 (3–65) versus PDT 3 (3–45), (P &gt; 0.519).</td>
</tr>
</tbody>
</table>

AE = adverse event; ALA = aminolevulinic acid; EOS = end of clinical study; FUP = follow-up; HAL = hexaminolevulinate; IQR = interquartile range; MAL = methyl aminolevulinate; NA = not available; NRS = numeric rating scale; PDT = photodynamic therapy; SD = standard deviation; SE = surgical excision; TEAE = treatment emergent adverse event; VAS = visual analog scale; 5-FU = 5-Fluorouracil.

were observed. The AFXL pre-treatment did not influence pain sensation during illumination [57].

Conclusions

According to the data reviewed, both ALA-PDT and MAL-PDT can be termed as generally effective and well-tolerated treatment modalities for the treatment of thin and small sBCC and nBCC. In terms of efficacy, similar CR were observed between PDT and most of the other interventions, except for SE and imiquimod which demonstrated better results [36-41,51-54,56]. The main weakness of surgery, especially when compared to PDT, was the cosmetic outcome, with PDT being superior and exhibiting more often good or excellent aesthetic results. Pain during intervention was higher with PDT [41,51-54,56]. PDT was more effective than placebo for nBCC [55]. No major differences were observed between MAL-PDT and ALA-PDT in terms of efficacy, AEs, pain and cosmetic outcomes for sBCC in 3 RCTs implying their equality [33-35,45]. The combination of imiquimod with ALA-PDT showed promising results but with a short-term follow-up in one study [49]. Interestingly, the laser pretreatment along with PDT combination showed favorable outcomes and good clearance rates in 3 studies with nBCC. Despite that, further comparative clinical testing is necessary to achieve more clarity [50,57,58]. Cryotherapy yielded better results regarding CR than PDT in one study with a 12m follow-up [46], while in another with a 5 year follow-up, it did not [48]. For sBCC, different illumination protocols that were tested showed that a regimen of a double illumination at 4 and 6 hours after application of ALA was more effective than a single illumination protocol, while both exhibited a good safety profile. Those regimens however require longer hospital visits which could affect patient adherence negatively [43,44].

For most studies the main concern with PDT, was the pain and feeling of discomfort that was experienced during and/or immediately after illumination. In most cases though, it was well tolerated without the administration of analgesic medication. In the rare cases of intolerable pain during treatment, medication can be offered in order to achieve pain relief. A wide range of treatment-related AEs were observed including erythema, edema, pruritus, crusting and vesication with most to be of mild or moderate severity and usually self-limiting. No life-threatening AEs were attributed to
PDT and no substantial dropout rates were detected during the observation period. These data suggest that PDT exhibits a very good safety profile with the only concern to be the treatment-related pain. PDT exhibited favorable aesthetic results in the various studies, assessed by both patients and physicians in some, and especially in comparison to different treatments.

Main limitations of some of the examined studies were the small number of participants, a follow-up of less than 12 months, the heterogeneity of the assessment of clinical outcomes and that not all studies reported treatment-related AEs. The follow-up duration was important for the assessment of efficacy of the various treatment modalities since lesions may recur years after treatment and thus short-term follow-ups could be misleading. In addition to that, lesions that did not respond to therapy were in some cases misdiagnosed as nodular or superficial RCCs when in fact they were a more aggressive subtype which required a different therapeutic approach. This supports the need of biopsy for the evaluation of treatment response, especially for recurrent or residual lesions, while clinical assessment and dermoscopy as diagnostic and assessment tools have some limitations. For the assessment of pain, AEs and cosmetic outcomes shorter duration of observation is generally sufficient although some of the examined studies provided long term results.

Our data suggest that PDT poses as a great tool among the various available treatment modalities for the treatment of small and thin sBCC and to a lesser extent nBCC. Since many alternatives exist, with comparable efficacy, patient preference should be taken under consideration. After thorough patient assessment, PDT should be considered the first option for select patients with special concerns about the cosmetic results, long lasting and unwanted AEs, with multiple lesions, and with evident contraindications to surgery and the other alternatives including previous allergic and topical reactions. Further research in clinical and preclinical settings is warranted since novel approaches such as lasers, novel lightning sources, different illumination protocols and different combinations of PDT with other treatments could improve responses to therapy and eventually patient care.

References


Oral Diseases During Systemic Psoriatic Drugs: A Review of the Literature and Case Series

Annunziata Raimondo¹, Federica Di Spirito¹, Serena Lembo¹

¹ Department of Medicine, Surgery and Dentistry, “Scuola Medica Salernitana”, University of Salerno, Italy

Key words: psoriasis, anti-psoriatic drugs, oral health, oral adverse drug reactions


Accepted: November 29, 2023; Published: April 2024

Copyright: ©2024 Raimondo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Annunziata Raimondo, M.D., Research Fellow, Department of Medicine, Surgery and Dentistry, “Scuola Medica Salernitana”, University of Salerno, Salerno, Italy. E-mail: araimondo@unisa.it

ABSTRACT

Introduction: The oral health of psoriatic patients seems to be compromised compared to that of control individuals: many published studies have investigated the relationship between psoriatic disease and gingivitis, periodontitis, and missing teeth. However, data from these studies are not consistent nor exhaustive. Moreover, no study has considered the possible specific effects of conventional and biological systemic psoriatic treatments.

Objective: We report a narrative review of the literature about the possible link between anti-psoriatic drugs and oral disease onset and present case series of patients that have experienced oral disease during systemic therapy for psoriasis.

Methods: This is a narrative review. The literature search was performed using the MEDLINE database. From the selected articles, additional references were identified by a manual search among the cited literature.

Results: Oral adverse events during psoriatic therapies can be found in sporadic cases. The specific mechanisms of interplay between oral anatomic structures and the pathway targeted by the systemic agents will be investigated in depth.

Conclusion: All psoriatic patients who are candidates for conventional or biological systemic therapy should have regular oral health check-ups with a dentist and a dermatologist to prevent oral complications. Dermatologists and oral medicine specialists should be ready to recognize and manage this increasing number of oral adverse drug reactions during systemic treatments for psoriatic disease so as to provide patients with sufficient information about this risk and to stress the fundamental importance of regular dental assessments and good oral hygiene.
Introduction

Psoriatic disease is a complex and multifactorial disorder with systemic involvement and auto-inflammatory pathogenesis [1]. Oral psoriatic lesions do not follow a predictable pattern: angular cheilitis and fissured white-coated geographic tongue lesions are examples of oral clinical manifestations associated with psoriasis [2, 3]. Patients with psoriasis also have an increased risk of developing other illnesses, such as inflammatory bowel disease, cardiovascular disease, metabolic syndrome, and diabetes as well as articular and bone inflammation [2-6]. Moreover, many published studies have reported that oral health in psoriatic patients seems to be compromised compared to that of control individuals. Based on a recent meta-analysis, periodontal disease is more frequent in psoriasis patients, with a reported statistically significant increase in odds ratio, with differing severity [7]. Psoriasis represents a risk factor for periodontitis in these patients. Although there are similarities in the risk factors and comorbidities between psoriasis and periodontal disease, their relationship's pathophysiology is still speculative [2, 8]. Current systemic therapeutic strategies, including disease-modifying anti-rheumatic drugs (DMARDs) and biological agents, permit the almost or complete clearance of psoriatic skin manifestations, with an improvement in quality of life. Biological agents are categorized by their target in anti-TNF-α, anti-IL17, and anti-IL23. Moreover, oral therapy for psoriatic disease is available: an inhibitor of the enzyme phosphodiesterase E4 (PDE4). The possible specific effects on the oral health of DMARDs, biologics, and small-molecule systemic psoriatic treatments are underestimated and reported as sporadic cases in the literature.

Objective and Methods

The purpose of this narrative review was to collect the literature on this topic, focusing on studies that describe oral adverse drug reactions (ADRs) in the context of systemic drug therapy for psoriasis. The literature search was performed on MEDLINE via PubMed and Google Scholar databases using these search terms: “oral diseases,” “psoriasis,” “psoriatic systemic drugs,” “biologic therapy,” and “oral adverse event,” with diverse matches among them. The inclusion criteria were all types of articles indexed on PubMed and related to psoriatic patients. The exclusion criteria were full text not available and not in English. From the selected articles, additional references were identified by a manual search among the cited literature.

Moreover, we report a case series of psoriatic patients that have experienced oral disease during anti-psoriatic systemic therapies.

DMADRs, Psoriasis, and Oral Disease

Conventional systemic therapies are used to treat moderate-severe psoriatic patients who are not responsive to topical medications and/or to phototherapy. These therapies include acitretin, cyclosporine, and methotrexate.

Acitretin

This is an oral retinoid, which is a synthetic form of vitamin A, and it is approved to treat psoriasis. Possible side effects are hair loss, dry skin and eyes, increased sensitivity to sunlight, peeling fingertips and nail changes, depression, headache, and decreased night vision. Regarding potential oral ADR, chapped lips and dry mouth are common, as are bleeding gums [9]. There are few data in the literature about other oral ADRs in psoriatic patients during acitretin therapy. However, we report two cases of destructive periodontitis resulting in tooth loss.

Case 1

A 52-year-old female with severe recalcitrant palmpoplantar psoriasis was started on 25 mg of acitretin daily. She is a smoker and had a personal history of periodontal disease in follow-up. After two months, clinical psoriatic manifestations significantly improved, but the patient experienced a rapid worsening of her periodontal status with the loss of three teeth of the lower arch.

Case 2

A 53-year-old female with moderate psoriasis localized at the palmpoplantar, elbow, and pretilbial areas was started on 25 mg of acitretin daily. She is a heavy smoker (about 15 cigarettes per day). After one month, as she achieved a good clinical response, the dosage was reduced to 20 mg/day. However, after three months, the therapy was discontinued due to the onset of significant side effects, including telogen effluvium, dyspepsia with weight loss (about 14 kg in 6 months), acute sacroiliitis, and a rapid worsening of pre-existing chronic periodontitis that led to the loss of five upper jaw teeth. After discontinuing acitretin, the patient started a biological drug.

Cyclosporin

Cyclosporin (CsA) is an immunosuppressive drug approved for the treatment of moderate-to-severe psoriasis. The most common side effects are decreased kidney function, headache, high blood pressure, the elevation of cholesterol serum level, hypertrichosis, and tingling or burning of the arms or legs. The most common oral ADR is gingival hyperplasia, reported in about 15% of psoriatic patients and in up to 80% of transplant patients [10]. This well-recognized ADR is not related to the dose or to the duration of treatment. Predictive
factors are the level of dental plaque and gingival inflammation. For this reason, correct oral hygiene and meticulous plaque control are indispensable to prevent this ADR. Dermatologists should be more sensitive to this aspect, and they should recommend the patient to consult a dentist before starting CsA therapy to correct some risk factors, such as appropriate oral hygiene, smoking cessation, adequate diet, and possible concurrent medication interaction. The combination of CsA and nifedipine exponentially increase the severity of gingival hyperplasia. Interestingly, it has been shown that females have a higher risk of developing ADRs during CsA therapy [17]. Female physiology, such as hormonal status and menopause, seems to have an important role that should be considered; hormonal changes are reflected in differing oral health related to estrogen and progesterone levels. It has been supposed that menstrual cycles, pregnancy, and menopause influence drug pharmacokinetics and pharmacodynamics, with an effect on its tolerability [11].

**Methotrexate**

Methotrexate (MTX) is an antagonist of folic acid with immunomodulator action. At high doses, it is used as a chemotherapeutic drug, while at a low dose (no more than 25 mg/week), it has anti-inflammatory effects, and it represents a valid therapeutic option for many inflammatory disorders. The addition of folic acid is the most important antidote to managing acute MTX toxicity, improving gastrointestinal tolerance, and preventing severe hematological disorders [12]. Regarding oral ADR, mucositis or oral ulcers are the most frequent events, which appear in 11-17% of MTX-treated patients [14,15]. The severity of these oral side effects of MTX can range widely, and it is seldom easy to treat them. What the most efficient care for patients with oral ulcers who take MTX at low doses is has been addressed by a systematic review of oral ulcers caused by low doses of MTX. The systematic review consists of sixteen research papers with a total of 24 individuals who experienced mouth ulcers while receiving low-dose MTX therapy. The mean patient age was 65.45 years, the mean MTX treatment duration was 52.91 months (SD: 80.75), and the average MTX dose was 10.93 mg/week (SD: 5.45). Except for one patient, all patients took MTX orally. The lingual dorsum, hard palate, gingiva, retromolar region, keratinized gingiva, and lip were the sites of the lesion. The lesions typically appeared after 35.63 days on average (SD: 52.57). The average recovery duration was 19.9 days (SD=10.63). Only three out of the 24 patients identified themselves as non-smokers. Moreover, only 50% of the patients mentioned using any concurrent medications. The most common management was MTX withdrawal and supplementation of folic acid, followed by only interruption of MTX. Some authors associated the abandonment of MTX with folic acid and systemic corticosteroid therapy.

Frequently, patients who experienced this ADR did not re-assume MTX. All these studies have many risks of bias, a lack of important information on patient history, and a short follow-up (the average follow-up period for these patients was 19.2 months, with an SD of 17.81). Moreover, differential diagnosis with other entities, including lichenoid reactions, is very difficult due to incomplete medical history. Indeed, overdosage and interactions with other medicines, particularly nonsteroidal anti-inflammatory medications, are the most frequent causes of MTX toxicity. Oral ulcers due to MTX therapy is an ADR that the specialists do not underestimate because these ulcers can be associated with a lymphoproliferative disorder, and they can cause malnutrition and the death of the fragile patient.

**Case 1**

We have previously described a 60-year-old female with palmoplantar psoriasis who was unresponsive to topical therapy and was switched to MTX 10 mg/week administered subcutaneously, along with 10 mg of folate the next day. The patient’s palmar-plantar psoriasis manifestations significantly improved three months later, but the challenge was managing the medication and concurrent SARS-CoV-2 vaccination. After that, we advised stopping MTX one week before and one week after receiving the COVID-19 vaccine. The patient experienced diffuse erythema over the entire body surface three days after the immunization, swelling on the right periorcular area and in the mouth, and ulcer on the soles of the her feet (Figure 1). Corticosteroids (40 mg/day) and antihistamines (10 mg/day) were then administered to the patient, with full recovery in one month [22].

**Case 2**

A 61-year-old female with plaque psoriasis, psoriatic arthritis, and mild comorbidities (hypertension and dyslipidemia) started methotrexate treatment at a dose of 15 mg/week plus 10 mg of folate the day after. However, after one month, the therapy was discontinued because of the emergence of numerous adverse outcomes like myalgia, pulpitis, and gingival bleeding. The patient experienced severe ulcerative gingival stomatitis with ulcers and erosions that affected the buccal mucosa, the gingiva, and the tongue. Clinical oral manifestations resolved after suspension of MTX and appropriate topical therapy with antiseptic and corticosteroid agents.

**Biological Agents, Small Molecules, Psoriasis, and Oral Disease**

Biological therapies are agents that have specific targets, including cytokines, receptors, and signaling molecules. They have revolutionized the therapeutic approach to psoriasis, obtaining clearance or near clearance of clinical manifestations. To date, the literature lacks documents that report
oral ADRs in the course of biological therapy for psoriasis. Many papers have described the possible link between psoriasis and periodontal disease (PD) but not the possible effects on the latest biological drugs. Recently, this aspect has been investigated in patients with rheumatoid arthritis (RA) suffering from concomitant PD in therapy with anti-TNF-α biologic agents (infliximab, adalimumab, etanercept, certolizumab pegol, golimumab) [16, 17]. These studies in accordance with the evidence that anti-TNFα inhibitors worsen periodontal parameters and gingival inflammation and slightly increase concentrations of antibodies against P. gingivalis. However, they decrease the gingival destruction of bone. A recent study reported that biological therapy, such as anti-TNF-α and anti-IL6 receptor therapy, may not lessen the severity of PD in RA patients and does not affect the activity of the disease. Interestingly, this study described a significant negative correlation between PD severity and the therapeutic response of RA patients: PD severity correlated with reduced effectiveness of the biological treatment. Consequently, PD therapy strategies may be helpful in enhancing RA patients’ therapeutic responses [26]. Another longitudinal observation study had as its objective to assess the effect of MTX and etanercept treatment on the periodontal condition of RA patients. The results showed that MTX or anti-TNFα treatment did not improve the periodontal condition, demonstrating a negligible influence [17-19]. Future large studies are needed to explore in depth the impact of anti-TNF therapies on PD, especially in the psoriatic population. Another important class of biological drugs is the anti-interleukins (IL), including anti-IL-17 and IL-23. They have a good safety and effectiveness profile for the treatment of moderate-severe psoriasis. Regarding the IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab) and oral ADRs, the most frequently reported event is Candida infection. This side effect is due to the important role that IL-17A plays in innate and adaptative responses against Candida infections. However, in most cases, the appropriate local and occasionally systemic antifungal therapy resolves the infection without biological drug withdrawal. According to a recent comprehensive study, individuals receiving brodalumab, secukinumab, or ixekizumab had a risk of developing a Candida infection of 4%, 1.7%, or 3.3%, respectively. The frequent localizations are oral and genital, with forms of mild to moderate severity [20]. Candida is a commensal, and many factors can promote its transition to a pathological condition. Recognizing predisposing factors (medical conditions, a prior history of recurrent oral candidiasis, etc.) and acting on them can reduce risk. There are reported cases of a severe form of candidiasis, such as the mucocutaneous form, and atypical clinical manifestations for which the differential diagnosis with leukoplakia, oral lichen planus, or non-specific lichenoid reaction is not easy and requires other diagnostic procedures, including biopsy [20, 21]. Considering the high prevalence of psoriatic diseases in the general population and the large group of patients who undergo biological therapy with these agents, a well-structured randomized control study is necessary to evaluate in depth the adverse effects of long-term IL-17 inhibitor therapy on oral health.

To date, no oral ADRs are reported in patients during anti-IL-23 biological therapies (guselkumab, tildrakizumab, risankizumab) as well as small molecule agents (apremilast).
is correlated to the increase in novel and unexpected ADRs, which need to be managed rapidly and appropriately. Psoriatic patients frequently have many comorbidities, such as psoriatic arthritis (PsA), which negatively affect oral health. In particular, the involvement of temporomandibular joint (TMJ) causes malocclusion, restricted jaw movement range, preauricular edema, and impaired eating function. The impact of this condition on the individual's daily life can be very negative and requires specific therapeutic actions [23]. Recently, the prevalence of atypical oral lesions in the course of conventional as well as biological therapies is enhanced, even if the specific mechanisms of interplay between oral anatomic structures and the pathway targeted by the systemic agents will be investigated in depth. Dermatologists and oral medicine specialists should be ready to recognize and manage this increasing number of oral ADRs during systemic treatments for psoriatic disease, providing patients with sufficient information about this risk and stressing the fundamental importance of regular dental assessments and good oral hygiene so as to avoid side effects (Table 1).

Conclusions and Perspectives

ADRs are potentially harmful side effects associated with the use of drugs. The growth of new target therapies for the management of autoimmune and autoinflammatory diseases is correlated to the increase in novel and unexpected ADRs, which need to be managed rapidly and appropriately. Psoriatic patients frequently have many comorbidities, such as psoriatic arthritis (PsA), which negatively affect oral health. In particular, the involvement of temporomandibular joint (TMJ) causes malocclusion, restricted jaw movement range, preauricular edema, and impaired eating function. The impact of this condition on the individual's daily life can be very negative and requires specific therapeutic actions [23]. Recently, the prevalence of atypical oral lesions in the course of conventional as well as biological therapies is enhanced, even if the specific mechanisms of interplay between oral anatomic structures and the pathway targeted by the systemic agents will be investigated in depth. Dermatologists and oral medicine specialists should be ready to recognize and manage this increasing number of oral ADRs during systemic treatments for psoriatic disease, providing patients with sufficient information about this risk and stressing the fundamental importance of regular dental assessments and good oral hygiene so as to avoid side effects (Table 1).

Table 1. Key considerations for conducting surveillance on oral health in patients with psoriasis.

| Regular Dental Check-ups and Oral Health Assessment | Encourage patients with psoriasis to schedule routine dental examinations with a dentist who is skilled in any potential oral health complications linked to the skin condition. The best frequency for these examinations should be twice annually. |
| Patient Education | Psoriatic patients should be informed by dermatologists and dentists about the value of maintaining proper oral hygiene. This includes using mouthwash, flossing, and brushing the teeth as prescribed. The possible effects of psoriasis and its therapies on dental health should also be discussed with patients. |
| Oral Hydration | Encourage patients to maintain adequate oral hydration to help avoid dry mouth, a problem that affects many people with psoriasis. It can be helpful to drink water throughout the day and, if necessary, to use substitutes for saliva. |
| Stress Management | Since stress can exacerbate both psoriasis symptoms and oral health problems, it is possible to advise psoriatic patients on stress management techniques. Stress-reduction strategies and exercises for relaxation can be helpful. |
| Patient Communication | Ensure that the patient, dermatologist, and dentist are in constant communication. For the proper course of action to be taken, patients should be encouraged to report any oral symptoms or discomfort as soon as possible. |
patients who receive conventional or biological systemic therapy should be meticulously examined by a dentist and dermatologist with regular follow-up to prevent oral health complications. Many risk factors are modifiable [24], such as oral hygiene, anti-septic agents, smoking cessation, and a diet rich in fruits and vegetables and low in fat and sugar. Gender attention is another important factor to consider in the management of chronic conditions such as psoriatic disease. Long-term studies should be done in the future to find out whether and how much an improvement in oral health connects with the course of psoriasis as well as whether and how much anti-psoriatic therapies affect oral wellbeing.

References


Efficacy of Intralesional Methotrexate Injection versus Triamcinolone Acetonide in Nail Psoriasis: A Systematic Review and Meta-Analysis

Stephanie Nathania¹, Diah Adriani Malik¹, Muslimin¹, Hardian²

¹ Department of Dermatovenereology, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital Medical Center, Semarang, Indonesia
² Department of Physiology, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital Medical Center, Semarang, Indonesia

Key words: methotrexate, triamcinolone acetonide, nail psoriasis


Accepted: December 12, 2023; Published: April 2024

Copyright: ©2024 Nathania et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Stephanie Nathania, Department of Dermatovenereology, Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital Medical Center, Jl. Dr. Sutomo No.16, 50244, Semarang, Indonesia. Phone: +62/81809013509
Email: stephanie.dvjuli18@gmail.com

ABSTRACT

Introduction: Psoriasis is a chronic inflammatory skin disease that can affect many parts of the body. Psoriatic involvement of the nail bed or nail matrix results in nail psoriasis, which is common. Patients with psoriatic nails have impaired quality of life due to the appearance of nails, and significant morbidity and functional impairments may arise in large cases. The management of nail psoriasis is challenging because it is usually time-consuming, with uncertain outcomes. The existing evidence suggests that intralesional injections are particularly effective for nail psoriasis. Current studies provide recommendations on the intralesional injection technique, recommending an optimal concentration of methotrexate (MTX), triamcinolone acetonide (TA), and cyclosporine, but the comparison of these treatments is still limited.

Objective: This study aimed to evaluate the efficacy of intralesional injections of MTX compared with TA in treating nail psoriasis using the Nail Psoriasis Severity Index (NAPSI) score.

Methods: A systematic literature search was performed on EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, and ClinicalTrials.gov using subgroups terms: “intralesional methotrexate injections for nail psoriasis,” “intralesional triamcinolone acetonide injections for nail psoriasis,” and “NAPSI Score.” Three studies were included in the qualitative synthesis and meta-analysis.
Introduction

Psoriasis is a chronic inflammatory skin disease with predominantly skin and joint involvement. Psoriatic involvement of the nail bed or nail matrix results in nail psoriasis. Nail psoriasis is more common in adults, with a prevalence of up to 10-78% [1]. It can manifest clinically as a wide variety of nail changes, like discoloration, subungual hyperkeratosis, pitting, onycholysis, and splinter hemorrhaging of the nail bed, depending on the part of the nail unit affected. The most observed forms are psoriasis of the nail matrix, nail bed, and nail fold. Patients with psoriatic nails have impaired quality of life due to the appearance of nails, and significant morbidity and functional impairments may arise in large cases [2, 3].

The management of nail psoriasis is challenging because it is usually time-consuming, with uncertain outcomes. The treatment options mainly depend upon the severity and extent of disease. Patients with nail psoriasis are treated with either topical, intralesional, or systemic therapies [4]. Methotrexate (MTX), acitretin, and leflunomide are the options for systemic therapy of psoriasis but, as they result in mild improvement of nail psoriasis, many experts consider systemic treatment inadequate for treating nail psoriasis. Topical therapy represents one of the oldest and most well-studied treatment methods for nail psoriasis. Multiple medications have been studied, including corticosteroids, calcipotriol, tazarotene, 5-fluorouracil, cyclosporin, psoralene, and topical calcineurin inhibitors. However, achieving optimal therapeutic concentrations of topical medications is challenging with nail psoriasis given the presence of the nail plate, which can serve as an impermeable physical barrier. The existing evidence suggests that intralesional injections into the nail bed and matrix are particularly effective for alleviating lesions caused by psoriasis of the nail matrix and also have moderate effects on nail bed signs [5]. Current studies provide recommendations on the intralesional injection technique, recommending an optimal concentration of triamcinolone acetonide (TA), methotrexate (MTX), and cyclosporine [6]. Mittal et al. compared MTX with other active treatments such as TA and cyclosporine (CsA); good outcomes were reported for TA and MTX, which both appeared to be better than cyclosporine. Both TA and MTX acted as anti-inflammatory, anti-proliferation, and immunosuppressive agents [7].

Objectives

This study aimed to evaluate the efficacy of intralesional injections of MTX compared with TA in treating nail psoriasis using the Nail Psoriasis Severity Index (NAPSI) score.

Methods

We conducted a systematic review and meta-analysis for the evaluation of treatments for nail psoriasis. This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009.

Literature Search

A computer-based literature search was performed to identify relevant articles publish on MEDLINE PubMed, EBSCOhost, Scopus, ProQuest, ScienceDirect, SpringerLink, Elsevier Clinical Key, Cochrane library, and ClinicalTrials.gov as well as hand searching from Indonesia libraries. The main search terms using medical subject headings (MeSH) to create subgroups terms were: “intralesional methotrexate injections for nail psoriasis,” “intralesional triamcinolone acetonide injections for nail psoriasis,” and “NAPSI Score.”

Study Selection

The inclusion and exclusion criteria were determined before the search. The included studies fulfilled the following inclusion criteria: (1) the study discussed intralesional MTX and TA injections from 2018 until 2022; (2) study design was clinical trials with/without randomization; (3) the study participants should not have received systemic or topical therapy within 3 months; (4) the evaluated interventions included 3-4 intralesional MTX injections or intralesional MTX injections for 4-6-week interval; (5) the outcome of the studies was reduction in NAPSI score.

Data Abstraction

Three independent reviewers abstracted data using a pre-defined data extraction form. The following information was extracted from each study: author, year of publication,
design of study, blind time period, patient type, details of the interventions (intraloesional MTX and TA injections), and the improvement after the treatment using NAPSI score.

Data Analysis

We performed statistical analyses using the Cochrane systematic review software (Review Manager (RevMan) [Computer program] Version 5.4.1., 2020). Categorical data are displayed as percentages, and numerical data are displayed as mean and standard deviation (SD). The meta-analysis assessed the weighted mean between changes in the mean and SD from baseline of the treatment groups and control groups.

Results

Systematic Review

We identified 51 articles matching the search criteria. We extracted 42 articles after reading the title and removing duplicate publications. After reading the abstract, 18 articles were excluded. Furthermore, we retained 33 articles after a full-text review. Three complete articles were assessed for eligibility in order to evaluate the efficacy of MTX intraloesional injection as the treatment of nail psoriasis in qualitative and quantitative synthesis. The literature search was conducted based on the PRISMA flow diagram (Figure 1) [7].

These three studies included 38 patients and were conducted in India (n=1), Egypt (n=1), and Italy (n=1). All of the included trials used the MTX intraloesional injection as the intervention and TA intraloesional injection for the control group. Two of the trials used De Beker injection technique in four injection sites. One of the trials used V-shaped injection technique in two injection sites. The duration of the intervention in all of the trials was 24 weeks.

Results of Qualitative Data Analysis

1. Starace et al., 2022

A study by Starace et al (2022) assessed a pilot study that compared intraloesional methotrexate injections versus triamcinolone acetonide in patients affected by nail matrix psoriasis. The study participants were enrolled in Italy between January 2019 and September 2020. Participants included a total of 12 patients with 20 nails affected with psoriasis who had not received any treatment in three months. Patients were divided into two groups of six patients each: Group 1 was treated with MTX 25 mg/mL and Group 2 with TA 10 mg/mL. Each group had a baseline NAPSI score of 5.3. Depending on the group, either MTX or TA was injected into each affected nail, following the De Beker technique and without digital anesthesia. The patients were asked to take folic acid 5 mg once weekly (not on the day of injection) to reduce
enrolled. Ninety fingernails in 17 patients were assigned to three groups of thirty nails each and treated with intramatricial injections of triamcinolone acetonide (10 mg/ml), methotrexate (25 mg/ml), or cyclosporine (50 mg/ml), respectively. Digital nerve blocks with plain lignocaine (2%) were administered before intervention. A volume of 0.05 ml was injected from each lateral angle, forming a V. Two injections were administered into each treated nail, with an interval of six weeks.

The severity of nail psoriasis was evaluated using NAPSI score after 12 and 24 weeks. The NAPSI score was graded as: G0 = No improvement; G1 = 25%–50% improvement; G2 = 51%–75% improvement; G3 = 76%–99% improvement; G4 = Complete recovery. At the end of the study, 15 patients (50%) from the TA group, 17 patients (56.7%) from MTX group, and 10 patients (33.3%) from the cyclosporine group showed G3 and G4 improvement. In the cyclosporine group, 11 patients (36.7%) showed only G2 improvement at 24 weeks.

This study showed that intramatricial injection therapy was a safe, economical, simple, and effective modality in the management of nail psoriasis. Pain, the most common side effect, was transient with injections of MTX and TA in this study, but with CsA injections, pain was severe and lasted for a few hours in about 50% of nails and for 2–3 days in eight nails injected with cyclosporine. In this study, MTX-associated adverse events (AEs) and toxicities. Patients were treated every six weeks for 24 weeks (total of four treatment sessions) and followed up for an additional six months.

Assessment by NAPSI was performed during each treatment session and at each follow-up visit. At the end of the four sessions, all patients showed improvement in their nail psoriasis, and no new nail disease was noted: mean NAPSI at one month after the last treatment session had a mean value of 0.3 for the MTX group and 1.8 for the TA group. These data were confirmed at the 6-month follow-up for MTX. All patients were satisfied with the procedure. Side effects included procedural pain, which was tolerable. Subungual hematoma occurred in one patient treated with MTX and in one patient treated with TA. Hypopigmentation of the proximal nail fold was instead reported in two of the six patients treated with TA. No major AE was reported in this study.

2. Mittal et al., 2018

The study by Mittal et al. (2018) assessed an open-label comparative study of triamcinolone, methotrexate, and cyclosporine. The study participants were enrolled in India in 2018. Patients having at least three affected fingernails with or without concomitant skin lesions who had not been on any systemic and topical antipsoriatic medications for at least the previous three months were

### Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>No</th>
<th>Researcher and year</th>
<th>Location</th>
<th>Final sample size</th>
<th>Treatment Protocol</th>
<th>Treatment group</th>
<th>Control group</th>
<th>Study Outcome</th>
<th>Duration</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mittal et al., 2018 [7]</td>
<td>India</td>
<td>17</td>
<td>MTX intralesional injection 2.5 mg/nail in the nail matrix, given in 6-week intervals</td>
<td>TA intralesional injection 2.5 mg/nail in the nail matrix, given in 6-week intervals</td>
<td>NAPSI Score</td>
<td>24 weeks</td>
<td>Open-label Comparative Study</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Abdelmeniem et al., 2022 [9]</td>
<td>Egypt</td>
<td>15</td>
<td>MTX intralesional injection 10 mg/nail in the nail matrix and nail bed, given in 4-week intervals</td>
<td>TA intralesional injection 4 mg/nail in the nail matrix and nail bed, given in 4-week intervals</td>
<td>NAPSI Score</td>
<td>24 weeks</td>
<td>Pilot Study</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Starace et al., 2022. [10]</td>
<td>Italy</td>
<td>6</td>
<td>MTX intralesional injection 10 mg/nail in the nail matrix and nail bed, given in 6-week intervals</td>
<td>TA intralesional injection 4 mg/nail in the nail matrix, given in 6-week interval</td>
<td>NAPSI Score</td>
<td>24 weeks</td>
<td>A Comparative Study</td>
<td></td>
</tr>
</tbody>
</table>
though the differences in the efficacies of intramatricial TA, MTX, and CsA were not statistically significant, MTX yielded the best results, with the maximum number of nails showing complete recovery (G4 improvement).

3. Abdelmeniem et al., 2022

A comparative study by Abdelmeniem et al. (2022) evaluated the efficacy of topical calcipotriol combined with urea 20% versus intramatrical injection of triamcinolone acetonide, 5-fluorouracil, and methotrexate in the treatment of nail psoriasis. The study participants were enrolled in Egypt in 2022. This study included 60 patients with nail psoriasis who were randomly assigned to four groups, each containing 15 patients. The first three groups received intramatrical injection of 0.1 ml of 5-FU (group A), MTX (group B), and TA (group C) into the nail matrix and bed monthly for three months. Group D received a topical combination of calcipotriol/urea 20% twice daily for three months. Patients that received intramatrical injections were anesthetized with a combination of topical lidocaine and prilocaine cream 30 minutes before injection. Four injections were administered: two injections at the nail matrix and two injections in the nail bed. The injections were administered twice a day for three months and followed up after six months. Therapeutic response was assessed every month for three months using the NAPSI score.

At the end of the study, the mean percentage of improvement was significantly higher in topical calcipotriol/urea combination (57.1 ± 26.4) than intramatrical TA (44.2 ± 32.7), intramatrical MTX (37.7 ± 14.2), and intramatrical 5-FU (29.6 ± 14). Adverse effects were mild and insignificant in the studied groups. In this study, topical calcipotriol/urea combination seemed to be more effective and safer than intramatrical injections of 5-FU, MTX, and TA.

### Results of Quantitative Data Analysis (Meta-Analysis)

The difference in mean NAPSI scores after MTX and TA intramatrical injections is shown in Table 2. All of the studies reported a reduction in NAPSI score in both the MTX group and the TA group.

The results of the meta-analysis of the effect of MTX intramatrical injection therapy compared to TA intramatrical injection therapy are shown in Figure 2. The heterogeneity test obtained $Q$ value $= 2.066; df=2; p<0.356$, $I^2=3.201$. This indicated that the data were homogenous, and the analysis was assessed in fixed effects model.

The results of the meta-analysis showed an overall difference in NAPSI scores after administration of intramatrical injection of MTX and TA that was $-0.213±0.232$ (95% CI: $-0.667$–$0.241$). This showed that the reduction in NAPSI score after MTX intramatrical injection was greater than that after TA intramatrical injection. The $Q$ statistic value was $z$ value $= -0.921$ (p=0.357), showing an insignificant difference

### Table 2. The difference in mean NAPSI score after MTX intramatrical injections (n=38) and TA intramatrical injections (n=38).

<table>
<thead>
<tr>
<th>Study</th>
<th>Methotrexate Mean±SD</th>
<th>Control Mean±SD</th>
<th>n</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Starace (2022)</td>
<td>5.33±1.80</td>
<td>0.33±0.47</td>
<td>6</td>
<td>5.33±1.70</td>
</tr>
<tr>
<td>Mittal (2018)</td>
<td>4.33±1.37</td>
<td>1.29±0.75</td>
<td>17</td>
<td>4.06±1.55</td>
</tr>
<tr>
<td>Abdelmeniem (2022)</td>
<td>6.70±1.10</td>
<td>4.3±1.4</td>
<td>15</td>
<td>6.5±1.70</td>
</tr>
</tbody>
</table>

Figure 2. Forest plot showing the efficacy of MTX intramatrical injection compared with placebo from all studies that were evaluated in the meta-analysis. 95% CI = 95% Confidence Interval;
in the effectiveness of intralesional MTX injection compared to TA in the management of nail psoriasis.

**Risk of Bias in Included Studies**

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system. The studies by Starace et al. and by Mitral et al. showed the possibility of risk of bias, while the study by Adelmeniem et al. showed a low risk of bias. Overall, the result of the meta-analysis evaluating the efficacy of MTX versus TA injection in nail psoriasis treatment was considered to be of moderate-quality (⊕⊕⊕).

Moderate-quality evidence indicated that there was a moderate level of confidence in the estimated effect size from the meta-analysis, where the actual effect size was likely to be close to the estimated value, although there was a possibility that the actual effect size was substantially different. Further studies are likely to have an important impact on the estimated effect size and the level of confidence in the estimated effect size.

**Discussion**

This was a systematic review and meta-analysis evaluating the efficacy of MTX versus TA intralesional injection in treating nail psoriasis. Three studies were included in the qualitative review (systematic review), and all three could be reviewed quantitatively (meta-analysis) to determine the efficacy of MTX and TA intralesional injection in nail psoriasis treatment based on the changes in the NAPSI score.

Methotrexate (MTX) has been shown to improve NAPSI score in several studies. MTX is a folic acid analog that irreversibly binds to dihydrofolate reductase and blocks deoxyribonucleic acid synthesis. MTX acts as the anti-inflammatory, anti-proliferative, and immunosuppressant agent [11]. It is usually taken orally or administered by injection (intramuscular, intravenous, subcutaneous) and has several indications, including nail psoriasis. Current studies suggest injections of MTX (10–25 mg/ml) be administered every 4–8 weeks [11, 12].

Triamcinolone acetonide (TA) is a synthetic corticosteroid [13]. The existing evidence suggests that TA intralesional injections into the nail bed and matrix are particularly effective for alleviating lesions caused by psoriasis of the nail matrix, and they also have moderate effects on nail bed signs [14, 15]. TA acts as the anti-inflammatory, anti-proliferative, and immunosuppressant agent. Current studies suggest injections of triamcinolone acetonide (5–10 mg/ml) be administered every 4–8 weeks. Side effects after these procedures are well known [16]. Local side effects include telangiectasia, skin atrophy, subungual drug deposition, subungual or subcutis hematoma, pigmentation change, necrosis, and ulceration of the skin. Systemic side effect includes Cushing syndrome [12, 13].

Patients in the MTX group were expected to have lower NAPSI scores after the intralesional injection of MTX. All of the studies showed a reduction in NAPSI scores after the injection of MTX. Starace et al. reported reduction in NAPSI score in MTX group (−5±1.62), and there was no recurrence during the six months of follow-up [10]. Mittal et al. also reported a reduction in NAPSI score in MTX group after four weeks of follow-up. The reduction in NAPSI score was 3.04±1.19 and was statistically significant [7]. Lastly, Adelmeniem et al. also reported a reduction in NAPSI score in MTX group (−2.4±1.28) [9]. These findings were consistent with previous studies, which reported significant improvement in nail psoriasis receiving MTX intralesional injections [11-15].

Patients in the TA group were also expected to have lower NAPSI scores after intralesional injections of TA. All the studies showed a reduction in NAPSI scores after the injection of TA. Starace et al. reported a reduction in NAPSI score in the TA group (−3.5±1.48) during the six months of follow-up [10]. Mittal et al. also reported a reduction in NAPSI score in the TA group after 24 weeks of follow-up (−2.77±1.35) [7]. Lastly, Adelmeniem et al. also reported a reduction in NAPSI score in the TA group (−2.5±2.21) [9]. These findings were consistent with previous studies, which reported significant improvement in nail psoriasis receiving TA intralesional injections [11-15]. Various side effects of intralesional injection of steroids lead us to suggest that MTX intralesional injection is currently preferable in the treatment of nail psoriasis.

We initially suggested that the reduction in NAPSI score in the MTX group was greater than TA group. Starace et al. and Mittal et al. reported significantly greater reduction in NAPSI score after intralesional injection of MTX (Starace et al.: −5±1.62; Mittal et al.: −3.5±1.48) [7, 10]. Different outcomes were reported by Abdelmeniem et al.: the reduction in TA group (−2.5±2.21) was greater than in the MTX group (−2.4±1.28). However, Abdelmeniem et al. reported no significance in their findings [9].

The meta-analysis of the effect of MTX intralesional injection therapy on nail psoriasis treatment was statistically insignificant compared to TA intralesional injection. \(P=0.357\). The statistical analysis and meta-analysis in this study were limited because of the limited number of patients. Heterogeneity of the dosage, technique procedure, and frequency of the therapy that had not been standardized also affected the results of this study.

However, this study has some limitations, including the limited number of RCTs evaluating the administration of MTX and PRP injection in nail psoriasis, thus affecting the
limited number of participants in this study, and that some studies only presented their results in the form of boxplot graph without specifying the numerical value or assessed the treatment response using different scores, thus disqualifying that study from being included in the meta-analysis.

Conclusion

Both methotrexate and triamcinolone acetonide are effective in treating nail psoriasis based on the reduction in NAPSI score. However, larger studies with more participants are necessary to establish the optimal dosage, number and frequency of injections, and technique of injection. A standardized assessment score is also needed to obtain more accurate results.

Abbreviations:

MTX: Methotrexate

TA: Triamcinolone acetonide

NAPSI: Nail Psoriasis Severity Index

PRISMA: Preferred Reporting Items for Systematic Review and Meta Analysis

References

Tape Stripping — Searching for Minimally Invasive Biomarkers in Atopic Dermatitis

Weronika Zysk¹, Magdalena Trzeciak¹

¹ Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdansk, Poland

Key words: Atopic dermatitis, biomarkers, precise treatment, tape-strips

Citation: Zysk W, Trzeciak M. Tape Stripping — Searching for Minimally Invasive Biomarkers in Atopic Dermatitis. Dermatol Pract Concept. 2024;14(2):e2024123. DOI: https://doi.org/10.5826/dpc.1402a123

Accepted: February 4, 2024; Published: April 2024

Copyright: ©2024 Zysk et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: Both the authors have contributed significantly to this publication.

Corresponding Author: Prof. Magdalena Trzeciak, Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdansk, Smoluchowskiego 17 Street, 80-214 Gdansk, Poland. Tel. +48585844014; fax +48585844020 E-mail: mtrzeciak@gumed.edu.pl

ABSTRACT

Atopic dermatitis (AD) is nowadays entering a new era of more targeted treatments. However, to make personalized medicine, which we are currently striving for, a reality, a reliable set of validated biomarkers is needed. The most practical seem to be biomarkers that can be obtained easily and minimally invasively. Tape stripping (TS) is a method that provides such an opportunity. This review summarizes the potential biomarkers of AD identified by the minimally invasive TS method. Thymic stromal lymphopoietin (TSLP), interleukin (IL)-13, CC chemokine ligand 17 (CCL17)/thymus and activation-regulated chemokine (TARC) and stratum corneum (SC) lipids can be used as predictive biomarkers for AD occurrence. CCL17/TARC also holds great promise for being reliable biomarkers for AD severity as well as treatment response. Nitric oxide synthase 2 (NOS2)/inducible nitric oxide synthase (iNOS) which high expression is specific for psoriasis may be a good biomarker for differential diagnosis between psoriasis and AD in challenging clinical situations. AD children with food allergy (FA) have a unique endotype characterized by selectively altered expression of various molecules in the skin that can indicate FA coexistence. Unfortunately, although numerous potential biomarkers have been found, none of these candidates have been validated and implemented into routine clinical practice, which still separates us from the possibility of a precise approach to AD patients.

Introduction

Atopic dermatitis (AD) is a chronic and highly heterogeneous inflammatory skin disorder with severe itching affecting approximately 20% of children and up to 10% of adult patients worldwide [1]. The disease is characterized by different endotypes that drive specific phenotypes [2]. Multiple factors such as disease chronicity, age of onset, ethnicity,
immunoglobulin E (IgE) levels, filaggrin mutation status, and underlying molecular mechanisms orchestrate the phenotype of AD [2]. Immune polarization in AD is primarily towards Th2/Th22, with variable Th1 and Th17 components [2]. In the phase of acute lesions, which are erythematous, wet, and highly inflammatory, accumulation of cytokines from the Th2 and Th22 axes and, to a lesser extent, Th17 is observed [2]. With disease chronicity, lesions turn lichenified, dry, thick, and hyperpigmented, which is accompanied by the intensification of Th2 and Th22 responses with significant increases in Th1 cytokines but no further increases in Th17 cytokines [2]. Apart from the typical Th2/Th22-dependent immune response, adult AD patients exhibit greater expression of Th1 cytokines than pediatric AD patients, whereas pediatric AD patients have higher involvement of Th17 cytokines than adults [2,3]. Additionally, the morphology and distribution of AD lesions change as patients age [2,3]. Asian AD patients have higher Th17 and lower Th1 axis activations than European American AD patients, who are characterized by immune polarization mainly towards Th2, Th22, and Th1. African American AD patients exhibit primarily Th2/Th22 axis activation with parallel attenuation of Th1/Th17 [2,4]. According to the IgE levels, AD can be categorized into the IgE-high, extrinsic subtype presented in 80% of patients, and the IgE-normal, intrinsic subtype in the remaining 20% [2,3]. Moreover, extrinsic AD is associated with traditional immune polarization towards Th2, cosinophilia, personal and family atopic background, and a higher percentage of filaggrin (FLG) mutation, whereas greater Th1 and Th17/Th22 immune responses, delayed disease onset, preserved barrier function, and increased metal contact hypersensitivity characterize patients with intrinsic AD [2,3].

With the development of novel targeted, highly specific therapies for AD over the past few years, we are seeing a revolution in the field of treatment for this disease. However, due to the high heterogeneity of AD, we will not be able to fully benefit from these therapies, which are regrettably also very expensive, without a precise medical approach [2]. Therefore, it is essential to search for reliable biomarkers, based on which it will be possible to accurately stratify patients and then apply appropriate preventive strategies or therapy precisely tailored to the patient’s needs, resulting in a medical care system with higher efficacy, less risk to the individual, and lower overall costs [5]. In other words, a validated set of biomarkers is an essential instrument in the toolbox of precision medicine in AD. A recently published review article on behalf of the International Eczema Council highlights the great unmet need for minimally invasive biomarkers, which would enable the implementation of precision medicine in AD [6].

Tape stripping (TS) is a minimally invasive way of obtaining stratum corneum (SC) and some of the stratum granulosum (SG) samples using adhesive tapes. The technique is simple, painless, and causes neither bleeding nor scarring. It is only associated with mild discomfort and a temporary red mark on the skin [7]. SC samples collected by TS are suitable for detecting several biological entities such as proteins, proteases, lipids, and RNA, providing a wide range of immune and epidermal barrier biomarkers for both lesional and nonlesional skin [8]. Until recently, the only method to obtain biomarkers from the skin was through a painful and scarring skin biopsy, which may also be complicated by infections and poor healing [6]. TS technique appears to be a promising and reliable alternative to skin biopsies in evaluating skin biomarkers in AD patients, especially infants, in whom conventional, painful skin biopsy may be difficult to perform and practically contraindicated [9]. In addition, due to the non-invasive nature of TS, this technique allows repeated skin samples to be taken from the same patient in a short time for various purposes, such as therapy monitoring or clinical trials, and longitudinal studies [9]. Skin biopsies in these cases would be challenging. The main limitation of TS seems to be that only biomarkers present in or diffuse into the superficial layers of the epidermis can be captured [9]. Moreover, previous tape strip reports in AD described limited sample detection rates [6], but recently global transcriptomic studies in young children and adults with AD have shown improved rates of detection, which were almost 100% per sample and marker [10,11].

Objectives

In this review, we provide a summary of potential AD biomarkers identified by the minimally invasive TS method (Table 1).

Methods

A comprehensive search of the literature using the PubMed electronic database with the search queries ,,atopic dermatitis AND tape strips”, ,,atopic dermatitis AND tape stripping”, ,,atopic dermatitis AND potential biomarkers”, ,,atopic dermatitis AND biomarkers”, ,,atopic dermatitis and epidermal biomarkers”, and ,,atopic dermatitis AND minimally invasive biomarkers” was performed. The search period was from the inception of the database to 8 May 2023. Based on the title and abstract analysis, we included articles concerning the potential biomarkers in atopic dermatitis identified by the tape-stripping method. At this step, we excluded records not related to the topic, non-English manuscripts, personal opinions, and duplicates or related to skin biopsy instead of tape strips. After reading the full manuscripts, some were excluded (not relevant or providing information concerning only skin
biomarkers identified by skin biopsy instead of tape stripping). Finally, we also included other suitable records that we found by searching references through other articles we found. Potential minimally invasive skin biomarkers identified by tape stripping were analyzed and summarized.

**Results**

**Potential Biomarkers for AD Occurrence**

The identification of biomarkers that can select infants at risk of developing AD would allow the implementation of target preemptive interventions. Currently, the best-known risk factor for AD is FLG mutations, carried by approximately 10% to 40% of these patients [12]. A positive family history of atopic diseases [4]. Since, for instance, the application of emollients from birth has been proposed as a preventive measure in high-risk infants [13]. However, two recently published trials did not confirm that daily use of emollients during the first year of life prevents AD in high-risk children [14,15]. Perhaps we may also need additional preventive strategies for AD. However, to establish a primary prevention strategy, it is essential to find biomarkers that can predict the development of AD. The effective prevention of AD would undoubtedly represent an important public health breakthrough.

In the prospective birth cohort study, the expression of epidermal thymic stromal lymphopoietin (TSLP) was proposed as a potential early biomarker for predicting AD development in infants. Children with high TSLP expression at 2 months were 5.3 times more likely to develop AD by age 24 months (95% CI, 1.3-21.4) [16]. Berdyshev et al [17] indicated a panel of biomarkers that predicted the onset of AD by the age of 24 months with an OR of 54.0 (95% CI, 9.2-317.5). It was the combination of a positive family history of atopic diseases, high IL-13, high 26:1-SM, and low O30:0(C22S)-CER levels in skin tape strips [17]. Rinnov et al [18] found that children who developed AD in the first 12 months of life had an altered SC lipid composition. Among the examined lipid markers, reduced phytosphingosine level may serve as a single predictor of the occurrence of AD with a prediction accuracy of 75.6% [18]. Another study has shown that elevated CCL17/TARC levels in SC at 2 months of age increased the risk of AD development within the first 2 years of life (aHR: 1.85; 95% CI: 1.18-2.89; P = 0.007) [19].

Noteworthy, all of these studies focus on biomarkers that predict the development of AD in infants. Since we have learned that AD represents a disease that can occur at any age [20,21], the availability of biomarkers predicting adult-onset AD or AD in the elderly would be very useful.

Table 1. The table shows the molecules that were tested by the tape stripping (TS) method as potential biomarkers. So far, none of them has been validated and implemented in routine clinical practice.

| The potential biomarkers of atopic dermatitis (AD) identified by the TS method |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Biomarkers for AD occurrence | TSLP, a panel of biomarkers: positive family history of atopic diseases, IL-13, 26:1-SM, and O30:0(C22S)-CER; phytosphingosine, CCL17/TARC |
| Diagnostic biomarkers | IL-34, FLG, FLG2, LOR, FA2H, NOS2/iNOS |
| Biomarkers for AD severity | IL-18, CXCL8, VEGF-A, Flt-1, IL-33, IL-23p19, IL-19, S100As, PI3, IL-36G, DEFB4B, STAT3, IL-37, IL-17C, K16, IL-4R, CD11b, CD11c, CCL17/TARC, CTACK, IL-8, TSLP, CCL2, Hbb-2, VEGF, MIF, MMP12, ICOS, IL-13, CCL26, IL-22, IL-17F, IL-26, CAMP/LL-37, FOXP3 |
| Biomarkers of barrier function | TSLP, Gal-7, SERPINB3, TARC/CCL17, CCL22, IL-22, IL-17A, trihydroxy-linoleic acid |
| Biomarkers for monitoring treatment response | TARC/CCL17, IL-8, CSF1, CCL13, CCL23, KYNU, IL-6R, CCL20, IL-34, FABP7, NGF, IL-37 |
| Biomarkers for comorbidities (Food allergy) | TSLP, a panel of biomarkers for differential diagnosis between psoriasis and AD |

AD = atopic dermatitis; IL = interleukin; CCL = CC chemokine ligand; CXCL = C-X-C motif chemokine ligand; CSF1 = colony-stimulating factor 1; CTACK = cutaneous T cell-attracting chemokine; DEFB4B = β-defensin 4B; FABP7 = fatty acid binding protein 7; FA2H = fatty acid 2-hydroxylase; FLG = filaggrin; Flt-1 = vascular endothelial growth factor receptor 1; FOXP3 = forkhead box P3; Gal-7 = galectin-7; ICOS = Inducible T-cell COStimulator; hBD-2 = human b-defensin-2; KRT = keratin; K16 = keratin 16; KYNU = Kynureninase; iNOS = inducible nitric oxide synthase; S100As = S100 calcium-binding protein A; IL-37 = cathelicidin; LOR = loricrin; MIF = macrophage migration inhibitory factor; MMP12 = matrix metalloepptidase 12; NGF = nerve growth factor; NOS2 = nitric oxide synthase 2; PI3 = phosphoinositide 3-kinase; K16 = keratin 16; KYNU = Kynureninase; iNOS = inducible nitric oxide synthase; S100As = S100 calcium-binding protein A; IL-37 = cathelicidin; LOR = loricrin; MIF = macrophage migration inhibitory factor; MMP12 = matrix metalloepptidase 12; NGF = nerve growth factor; NOS2 = nitric oxide synthase 2; STAT3 = signal transducer and activator of transcription 3; TARC = thymus and activation-regulated chemokine; TSLP thymic stromal lymphopoietin; VEGF = vascular endothelial growth factor.
Moreover, childhood AD can have periods of long remission and then recur in later stages of life [20,21]. Such prognostic biomarkers would be also very helpful in terms of the prevention of AD.

Potential Diagnostic Biomarkers of AD

To date, the diagnosis of AD is most commonly based on Hanifin and Rajka criteria, which were primarily developed based on the pediatric population. The clinical picture of AD in adult patients is characterized by marked heterogeneity. Reliable biomarkers for the diagnosis are lacking, and a diagnosis of AD, especially adult-onset AD, can be challenging [20]. Furthermore, there is a range of diseases that can mimic AD in both children and adults [22]. For this reason, there are unmet needs for biomarkers to confirm the diagnosis or distinguish AD from other diseases with similar manifestations, which would be incredibly useful in challenging cases.

Guttman-Yassky et al [11] has described IL-34 as a perfect single-gene classifier to discriminate early-onset AD skin from normal skin with almost 100% accuracy. Moreover, they found that epidermal barrier markers, such as FLG, FLG2, loricin (LOR), and fatty acid 2-hydroxylation (FA2H), were also effective discriminators. A comprehensive transcriptome analysis in patients with AD and psoriasis identified nitric oxide synthase 2 (NOS2)/inducible nitric oxide synthase (iNOS) expression as a single gene biomarker that can differentiate these two conditions with 100% accuracy (AUC = 1.0) by quantitative PCR and almost perfectly (AUC = 0.97) using the RNA-seq data [10]. Psoriasis skin exhibited significantly elevated levels of NOS2/iNOS expression, whereas AD skin exhibited no discernible increase in expression [10]. Thus, the differential expression of NOS2/iNOS between psoriasis and AD skin suggests its potential utility as a valuable biomarker for distinguishing between these two dermatological conditions, particularly in challenging clinical situations.

The usefulness of TS for differential diagnosis in patients with overlapping features of AD and psoriasis also finds reflection in real-life clinical practice. In patient presenting with concurrent psoriasis and AD, the analysis of tape strips revealed pronounced expression of Th17-related products, along with NOS2/iNOS, which is specific for psoriasis, as well as Th2-related products characteristic of AD confirming the overlap of the two diseases. The coexistence of these two conditions was also previously confirmed by a skin biopsy [23]. This suggests that TP can serve as a diagnostic tool in challenging clinical situations, replacing the need for invasive skin biopsies to distinguish between AD and psoriasis. However, there are still numerous biomarkers differentiating AD from many other diseases that need to be discovered.

Potential Biomarkers for AD Severity

In the era of more targeted therapies for AD, knowing the exact severity of the disease seems crucial for planning the appropriate timing, and intensity of treatment.

In the study by McAleer et al [24], among the examined SC markers, the levels of IL-18, CXCL8, VEGF-A, and Flt-1 in non-lesional skin showed the highest correlation with AD severity and barrier function among AD infants [24]. The investigation by Guttman-Yassky et al [11] among children with early-onset AD showed the greatest number of significant correlations between disease severity and lesional biomarkers, including the expression of Th2 (IL-33, IL-4R) and Th17 (IL-23p19) cytokines, Th17/Th22 (IL-19, S100A8, S100A9, IL-36G, β-defensin 4B (DEFB4B), STAT 3, and cathelicidin LL-37), innate (IL-17C), hyperplasia (epidermal proliferation marker K16), Th2 (IL-4R), and cellular (CD11b and CD11c) biomarkers. In another assessment of biomarkers, the levels of CCL17/TARC, CTACK, IL-8, and IL-18 in both lesional and non-lesional tape-stripped skin were indicated as crucial biomarkers of AD severity in children [25]. Cytokines such as IL-8, IL-18, and TSLP have demonstrated a positive correlation with SCORAD in lesional AD skin in the study conducted by Lyubchenko et al [26]. Furthermore, IL-8 appears to be a useful biomarker of local severity in both acute and chronic AD lesions [27]. Hulshof et al [28] has pointed out CCL17/TARC, CXCL8, and CCL2 as the most promising biomarkers to assess the severity of AD in children. In non-lesional AD skin, all 3 biomarkers significantly correlated with objective SCORing AD (oSCORAD), whereas in lesional AD skin, only CXCL8 significantly correlated with oSCORAD. Clausen et al [29] found a significant positive correlation between hBD-2 in lesional skin and both disease severity (SCORAD) and skin barrier function (TEWL) [29]. VEGF has been proposed as an indicator of the acute inflammatory condition of skin lesions in patients with AD [30]. Macrophage migration inhibitory factor (MIF) was suggested to be a marker of the local severity of AD, as its level in SC significantly correlated with the severity of the local skin lesion [31]. Other suggested biomarkers by He et al in lesional skin that may reflect the clinical severity of AD (according to TSS and IGA score) included markers of general inflammation (matrix metalloproteinase 12 (MMP12)), T-cell activation (inducible T-cell COStimulator (ICOS)), Th2 (IL-13, CCL17/TARC, and CCL26/eotaxin-3), Th22 (IL-22), Th17 (IL-17F, IL-26, and cathelicidin antimicrobial peptide (CAMP)/LL37), and T-reg (FOXP3).

[10] CCL17/TARC may be useful in the evaluation severity of lesions of AD, especially in acute ones as its level in SC was strongly correlated with acute phase parameters of lesions such as erythema, edema/papule, and oozing/crusts but not with itching and excoriation or chronic parameters such as lichenification and xerosis [32]. Additionally, CCL17/TARC may be useful in the evaluation severity of lesions of AD, especially in acute ones as its level in SC was strongly correlated with acute phase parameters of lesions such as erythema, edema/papule, and oozing/crusts but not with itching and excoriation or chronic parameters such as lichenification and xerosis [32]. Additionally, CCL17/TARC may be useful in the evaluation severity of lesions of AD, especially in acute ones as its level in SC was strongly correlated with acute phase parameters of lesions such as erythema, edema/papule, and oozing/crusts but not with itching and excoriation or chronic parameters such as lichenification and xerosis [32].
TARC has been considered an indicator of AD's systemic disease severity, as it correlated with laboratory parameters reflecting the systemic severity of the disease, such as the serum IgE level and the blood eosinophil count [32]. It should be mentioned that serum CCL17/TARC levels according to AD severity in both adult and pediatric patients currently available [6].

Biomarkers of Barrier Function in AD
Sano et al [33] found that the TSLP expression level was correlated significantly with SCORAD and epidermal barrier functions, such as TEWL. Importantly, among items within SCORAD, a significant correlation was shown only with the itching score and xerosis score, which is regarded as a reflection of epidermal barrier dysfunction in AD [33]. According to these results, the hypothesis was put forward that the expression level of TSLP in SC might be a useful biomarker of AD severity, especially epidermal barrier status. In addition, it seems to be applicable for estimating the effects of the use of moisturizing products on skin dryness because, after treatment with moisturizer, the level of TSLP was reduced [33].

Using an in vivo model of skin barrier disruption, it has been shown that the level of galectin-7 (Gal-7), which plays a role in maintaining epidermal homeostasis, was significantly correlated with TEWL [34]. Skin tape strip proteomic analysis has shown that among 45 identified proteins in non-lesional AD skin, SERPINB3 expression had the highest positive correlation with TEWL, while KRT10 expression had the highest negative correlation with TEWL [35]. Lyubchenko et al [26] has found that the levels of CCL17, CCL22, TSLP, IL-22, and IL-17A in lesional AD skin positively correlated with skin TEWL measurements in the pediatric cohort. According to results obtained by Chiba et al, [36], the trihydroxy-linoleic acid levels in the SC significantly correlated with TEWL, which makes it another possible biomarker of barrier function in AD easily measured by TS.

Potential Biomarkers for Monitoring Treatment Response of AD
The effective treatment of AD is a highly desirable goal. According to the data, up to over 55% of adult patients with moderate to severe AD complain of inadequate disease control [37]. Considering the high heterogeneity of AD, the “one-size-fits-all” approach may not be successful in these patients because treatment response may differ depending on immune differences in particular AD endotypes/phenotypes [3]. Biomarkers for monitoring treatment response may provide objective information on how effective a particular drug is in each patient. This would have significance in terms of selecting appropriate therapies for patients and consequently ensuring successful treatment outcomes. We greatly need biomarkers predicting treatment response to a particular drug, which is essential in the current era of new targeted therapies in AD. Based on these biomarkers we would be able to identify patients who will likely benefit most from particular drugs and stratify them before treatment initiation.

The TS technique was applied to assess the effect of topical therapy in a few studies. The results put CCL17/TARC and IL-8 in the light of promising biomarkers for monitoring topical therapy effect. After 6 weeks of using emollient, CCL17/TARC, and IL-8 expression decreased in moderate AD patients, which was correlated with reduced disease severity [38]. Additionally, it has been demonstrated that the expression of IL-8 in SC was significantly reduced after topical corticosteroid treatment and correlated with visual improvements in symptoms of AD [39]. Moreover, TS may be useful for assessing treatment response to systemic targeted drugs such as dupilumab. He et al [40] found that many key immune proteins were significantly decreased in lesional skin after dupilumab treatment, further correlating with the improvement of clinical symptoms of AD, as measured by EASI. These included markers of immune cell infiltration such as macrophages (CSF1), immune markers related to Th2 (CCL13, CCL23), Th17 (KYN), and innate immunity (IL-6R) [40]. CCL20, IL-34, and FABP7 were also observed to be useful in monitoring therapeutic response to dupilumab treatment [41]. Quantitative analysis of nerve growth factor (NGF) in AD stratum corneum has found that the level of NGF reflects the severity of the disease and may also help assess the therapeutic effects of AD [42]. The expression of NGF has been significantly downregulated after antihistamine and/or topical steroid treatment and correlated with the decrease in the severity of AD lesions and laboratory severity parameters of the disease, such as eosinophil count, and LDH level [42]. IL-37, an anti-inflammatory cytokine, is also believed to be a reliable biomarker to monitor cutaneous therapeutic response. An association between SCORAD score improvement and up-regulation of IL-37 following treatment of mometasone has been observed [43].

TS method can be a useful tool for treatment response. Traditional monitoring methods for treatment response often rely on subjective assessments or clinical observations. TS method provides objective evidence of changes occurring in the skin, allowing for a more accurate assessment of the efficacy of a treatment and tracking changes over time. Furthermore, the procedure can be easily repeated at different time points to monitor the progression of treatment response over time. The data obtained from TS can help us make informed decisions about treatment regimens and determine whether to escalate or reduce the intensity of the treatment or change medications resulting in ultimately improved patient outcomes.
Potential Biomarkers for Comorbidities of AD

Patients with AD often have not only allergic comorbidities but also others such as neuropsychiatric, autoimmune, metabolic diseases, or cardiovascular diseases [44]. There is a great need to seek biomarkers associated with comorbidities in AD. Evaluation of candidate biomarkers for comorbidities in AD by TS is limited; there are a few reports regarding food allergy (FA) in AD patients.

Skin tape strip proteomic analysis has shown that AD children with FA have a unique endotype characterized by selectively altered expression of keratins, proteases, inflammatory mediators, alarmins, glycolytic enzymes, and antioxidant defense proteins in non-lesional skin in comparison to children without FA as well as nonatopic children [35]. FLG breakdown products FA together with keratin 5 (KRT5), KRT14, and KRT16 have been proposed as prognostic biomarkers for coexisting food allergy in children with AD [45].

Studies that identify candidates for biomarkers predicting the development of diseases such as neuropsychiatric, autoimmune, gastrointestinal, malignant, and cardiovascular in AD patients are generally underdeveloped [46]. Identifying who is at risk of comorbidity may ensure a more holistic approach to these patients and targeted preventative strategies development. Unfortunately, this ability remains a key unmet need in patients with AD.

Conclusions

Numerous potential biomarkers have been proposed as a result of extensive work. But so far, none of these candidates have been validated and implemented into routine clinical practice. Reliability, clinical validity, a high positive predictive value, prediction of the therapeutic response, and disease progression are the seven most essential features that future validated biomarkers should fulfill, according to members of the BIOMAP project [47]. Currently, CCL17/TARC holds great promise for being reliable biomarkers for AD severity as well as treatment response in children and adults. In Japan, CCL17/TARC serves as a useful clinical biomarker for monitoring treatment efficacy, and since 2008 its serum levels have been commercially measured under health insurance support [6]. The TS technique allows us to obtain this biomarker in a minimally invasive way, both in children and adults. Considering the complex and heterogeneous nature of AD, it appears that in clinical practice, we need multiple sets of biomarkers rather than a single biomarker. The concept of personalized medicine in AD seems to be within reach. However, reliable biomarkers are essential to moving a step forward, without which we won’t fully benefit even from the most expensive therapy.

References


A Systematic Review of Diagnoses with Rosettes Under Dermoscopy

May Alorainy1, Kendall Buchanan2, Tyler Nussinow3, Judy B. Rabinowitz4, Peggy Cyr5,6, Elizabeth V. Seiverling1

1 Tufts University School of Medicine, Department of Dermatology, Boston, Massachusetts, USA
2 Medical College of Georgia at Augusta University, Department of Dermatology, Augusta, Georgia, USA
3 University of New England College of Osteopathic Medicine, Biddeford, Maine, USA
4 Hirsh Health Science Library, Tufts University, Boston, Massachusetts, USA
5 Maine Medical Center, Department of Family Medicine, Boston, Massachusetts, USA
6 Tufts University School of Medicine, Department of Family Medicine, Boston, Massachusetts, USA

Key words: rosettes, four dot, dermoscopy, shiny white structures, systematic review


Accepted: January 17, 2024; Published: April 2024

Copyright: ©2024 Alorainy et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: Dr. Seiverling is a consultant for Melatech and for DermaSensor. Dr. Buchanan is a consultant for DermaSensor and SkinVest. Dr. Cyr is a consultant for DermaSensor. The rest of the authors have no conflict of interest to declare.

Authorship: All authors have contributed significantly to this publication. May Alorainy and Kendall Buchanan: first co-authors who contributed equally to this manuscript.

Corresponding Author: Elizabeth V. Seiverling MD, Tufts Medical Center 800 Washington Street Boston MA, 02111. Tel: 617-636-0156 Fax: 617-636-8316 E-mail: vseiverling@gmail.com

ABSTRACT

Introduction: Rosettes are a cluster of shiny white dots in the shape of a four-leaf clover seen under polarized dermoscopic light. Historically, rosettes were primarily reported in actinic keratoses and squamous cell carcinoma. However, rosettes have also been reported in other conditions.

Objectives: The objective of this systematic review to elucidate the breadth of diagnoses exhibiting this unique dermoscopic phenomenon.

Methods: A review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Literature searches were performed in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science, as well as a manual search of the reference lists of screened articles.

Results: A total of 73 articles met the inclusion criteria. Out of these, 47 distinct diagnoses with rosette were identified. Among neoplastic conditions, keratinizing neoplasms had the highest number of articles reported (N = 19). Discoid lupus was the most commonly reported diagnosis within the inflammatory category (N = 6). Molluscum contagiosum was the predominant diagnosis among infectious entities (N = 3), while acroangiodermatitis was the sole diagnosis reported in the vascular category (N = 1).
**Introduction**

Under dermoscopy, rosettes are a distinct type of white shiny structures characterized by a cluster of shiny white dots in the shape of a four-leaf clover. They are created by the presence of scale in the follicular ostia and can only be observed under dermoscopy when using polarized light [1]. Historically, rosettes were primarily reported as a finding in actinic keratoses (AKs) and squamous cell carcinoma (SCC) [2]. However, several reports demonstrated that rosettes are not specific to keratinocytic neoplasms and are rather encountered in many other conditions [3].

**Objectives**

The goal of this systematic review was to conduct a thorough examination of all reported entities with rosettes to elucidate the breadth of diagnoses exhibiting this unique dermoscopic phenomenon. Through our analysis, we aim to equip clinicians with the knowledge necessary to harness the diagnostic potential of rosettes in the evaluation of skin lesions and cutaneous eruptions.

**Methods**

A review was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4]. Literature searches were performed in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science, through April 24, 2023, as well as a manual search of the reference lists of full-text-screened articles. Keywords and subject heading terms used were: dermoscopy, dermatoscopy, trichoscopy, epiluminescence/skin surface microscopy, rosettes, four dot and four clod. Conference abstracts, studies based on reflectance confocal microscopy alone were excluded. No studies were excluded based on language, publication date, or patient age. Two reviewers independently performed data screening and extraction (MA and KB). Conflicts were resolved by discussion with a third reviewer (ES). The full MEDLINE search was conducted as detailed below:

Ovid MEDLINE(R) ALL <1946 to April 24, 2023>  
1 exp Dermoscopy/  
2 dermoscop*.mp.  
3 dermatoscop*.mp.  
4 trichoscop*.mp.  
5 (microscope or microscopes or microscopy or microcopies).mp.  
6 exp Microscopy/  
7 5 or 6  
8 skin surface.mp.  
9 epiluminescen*.mp.  
10 8 or 9  
11 7 and 10  
12 1 or 2 or 3 or 4 or 11  
13 rosett*.mp.  
14 Four Dot.mp.  
15 4 dot.mp.  
16 four clod.mp.  
17 4 clod.mp.  
18 13 or 14 or 15 or 16 or 17  
19 12 and 18

**Results**

A total of 73 articles met the inclusion criteria (Figure 1). The majority were case reports (N = 33), followed by observational cohort studies (N = 29), case series (N = 7), review articles (N = 3) and a single randomized controlled trial (N = 1). Out of these 73 articles, 47 distinct diagnoses were reported (Table 1). The diagnoses were categorized into four main groups: neoplastic processes accounted for 51.9% of the diagnoses, inflammatory conditions comprised 39.0%, infectious conditions made up 7.8%, and vascular conditions represented 1.30%. Among neoplastic cases, keratinizing neoplasms had the highest frequency of number of articles reported, these predominantly included AKs and SCC (N = 12) followed by basal cell carcinoma (BCC) (N = 6) and one report of basosquamous carcinoma (n=1). Within the inflammatory category, discoid lupus erythematosus (DLE) was the most commonly reported entity (N = 6). Molluscum contagiosum was the predominant diagnosis among infectious entities (N = 3), while acroangiodermatitis was the sole diagnosis reported in the vascular category (N = 1).

**Conclusions**

This systematic review identified a wide range of skin conditions which manifest rosettes under dermoscopy. As...
previously reported, rosettes are commonly found in keratinocytic neoplasms with most of the articles devoted to actinic keratosis and squamous cell carcinoma. Rosettes are also frequently present in BCC [5] and accounted for approximately 30% of articles on keratinizing neoplasms. Therefore, BCC should be considered when encountering rosettes in neoplastic processes.

In addition to AK, SCC and BCC, this review identified articles on rosettes in autoimmune diseases, sarcomas, skin infections, rosacea, scars and cysts. Of the autoimmune conditions with rosettes, DLE was the most common. Notably, SCC may develop within DLE lesions, therefore it is imperative to seek additional dermoscopic indicators of SCC beyond the presence of scale and rosettes [6]. The breadth of diagnoses with rosettes supports the lack of specificity of this dermoscopic finding. Furthermore, this review identified three reports on rosettes in molluscum contagiosum. A subsequent report on a child who had two fleshy papules with rosettes raised concerns about SCC, which led to the decision to perform skin biopsies. The biopsies ultimately confirmed the presence of molluscum contagiosum instead [7]. Increased awareness of the presence of rosettes in infectious conditions, such as molluscum, has the potential to improve diagnostic accuracy and reduce the number of biopsies performed in pediatric patients.

The study main limitation is that most of the reports included were single case reports restricting the generalizability of rosettes as a universal finding for all cases of each diagnosis.

Lastly, in this review we did not attempt to characterize rosettes based on quantity, distribution, or location. Most articles were case reports featuring single entities, with limited dermoscopic images and lacked descriptive details necessary for further characterization of rosettes. In our own observations, rosettes are commonly diffuse in actinic keratoses, but are few and randomly arranged in entities such as scars and molluscum contagiosum [7]. Additionally, knowledge of hair follicle size and distribution in different body sites could provide further insight into the distribution and appearance of rosettes in different entities. For example, Otberg et al reported the forehead has the highest follicular density compared to the trunk and extremities, and the calf showed the largest hair follicle diameter [8]. Expanding this insight may help explain the differences in the distribution, quantity, and size of rosettes on dermoscopy.

In sum, this study identified the breadth of conditions with rosettes and may aid clinicians when developing a differential diagnosis of a growth or an eruption with rosettes. Given the wide range of conditions which can exhibit rosettes, it is important to look for additional clinical and dermoscopic clues before rendering a diagnosis or deciding to pursue a skin biopsy.

Figure 1. Flow diagram of literature screening using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
<table>
<thead>
<tr>
<th>Diagnostic Entity</th>
<th>Total Number of Reports</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>AKs/SCCIS/SCC</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>BCC [5,21–25]</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Basosquamous carcinoma [26]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Melanoma [27]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>LPLK/Lentigo [28]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Macular seborrheic keratosis [29]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blue nevus [30]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Warty dyskeratoma [31]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Syringocystadenoma papilliferum [32]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Trichilemmal cyst [33,34]</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Milium-like cysts [35]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Trichoepithelioma [36]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Juvenile xanthogranuloma [37]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphomatoid papulosis [38]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mycosis fungoides [39]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T-cell pseudolymphoma [40]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Kaposi sarcoma [41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acroangiodermatitis [42]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Molluscum contagiosum [43–45]</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Leprosy [46,47]</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lupus vulgaris [48]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Scars (including cicatricial alopecia) [49–51]</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Keloid [52]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>COVID-19 associated chilblain lesions [33,54]</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lichen planus [55,56]</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lichen sclerosis [57,58]</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rosacea [59,60]</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DLE [61–66]</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Acute CLE [67]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic CLE [68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLE (all types) [69]</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Comedonal lupus [70]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chilblain lupus [71]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Granuloma annulare [72]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lichen amyloidosis [73]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pigmented purpura [74]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epidermolysis bullosa [75]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Progressive vitiligo [76]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Photo-contact dermatitis [77]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Apocrine hidrocystoma [77]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urticarial dermatitis [1]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dermatofibroma [1]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Melanocytic nevus [1]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dilated pore [1]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cyst [1]</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*The total number of articles differs from the total number of diagnoses as some articles reported on multiple entities with rosettes.

AKs = actinic keratoses; BCC = basal cell carcinoma; CLE = cutaneous lupus erythematosus; COVID-19 = coronavirus disease-2019; CR = case report; CS = case series; DLE = discoid lupus erythematosus; LPLK = lichen planus-like keratosis; O/C = observational/cohort; R = review article; RCT = randomized controlled trial; SCC = squamous cell carcinoma; SCCIS = squamous cell carcinoma in situ.
References


Pilomatricoma: Clinical, Dermoscopic Findings and Management in 55 Pediatric Patients and Concise Review of the Literature with Special Emphasis on Dermoscopy

Marco Adriano Chessa¹,², Maria Francesca Baracca¹,², Alice Nadia Rossi¹,², Bianca Maria Piraccini¹,², Vittorio De Pietro³, Valentino Marino Picciola⁴, Alessandra Gelmetti¹,², Iria Neri¹

¹Dermatology Unit - IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
²Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum University of Bologna, Bologna, Italy
³Dermatology Unit – Azienda Ospedaliera-Universitaria di Siena, Siena, Italy
⁴University of Bologna, School of Medicine and Surgery, Bologna, Italy

Key words: pilomatricoma in children, typical pilomatricoma, atypical pilomatricoma, dermoscopic findings in pilomatricoma, management of pilomatricoma in pediatric patients

Citation: Chessa MA, Baracca MF, Rossi AN, et al. Pilomatricoma: Clinical, Dermoscopic Findings and Management in 55 Pediatric Patients and Concise Review of the Literature With Special Emphasis on Dermoscopy. Dermatol Pract Concept. 2024;14(2):e2024140. DOI: https://doi.org/10.5826/dpc.1402a140

Accepted: January 3, 2024; Published: April 2024

Copyright: ©2024 Chessa et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Maria Francesca Baracca, via Massarenti 9, 40138 Bologna, Italy. Telephone/fax: +390512144843 E-mail: maria.baracca@studio.unibo.it

ABSTRACT

Introduction: Pilomatricoma is a benign adnexal dermal or subcutaneous tumor derived from immature hair matrix cells.

Objectives: The aim of our study is to evaluate clinical and dermoscopic features of pilomatricomas, with a specific focus on pediatric lesions, and to provide a concise review of the existing literature.

Methods: A single-center retrospective study was undertaken on 55 patients with a histopathological diagnosis of pilomatricoma referred to the Dermatology Unit, University of Bologna, Bologna, Italy, between 2005 and 2023. Pilomatricomas were retrospectively evaluated relying on clinical and dermoscopic images. A PubMed search was conducted. All the relevant research up to July 31, 2023, was reviewed. We classified the cases as “typical” or “atypical” based on whether they were suspected of being pilomatricomas or not.
Introduction

Pilomatricoma, also called “calcifying epithelioma of Malherbe” or “pilomatrixoma”, is a benign adnexal dermal or subcutaneous tumor derived from immature hair matrix cells. It was first described in 1880 by Malherbe and Chenantais and, in 1961, Forbis and Helwig coined the term “pilomatrixoma” [1,2].

This tumor typically affects individuals during their first two decades of life. Clinically, it usually manifests as a firm, deep nodule, with a diameter ranging from 3-30 mm, mainly on the upper body.

Although the pediatric onset is the most common, dermoscopic features are primarily reported in adult lesions and only a few cases of pediatric patients have been described in the literature (Table 1) [3-13].

Objectives

The aim of our study is to evaluate both typical and atypical clinical and dermoscopic features of pilomatricomas, with a specific focus on pediatric lesions, and to provide a concise review of the existing literature.

Methods

A single-center retrospective study was conducted on 55 patients with a histopathological diagnosis of pilomatricoma referred to the Pediatric Dermatology Unit, University of Bologna, Bologna, Italy from 2005 to 2023.

Pilomatricomas were retrospectively evaluated by four dermatologists with expertise in dermoscopy and pediatric dermatology, relying on clinical and dermoscopic images only, and not allowed to consult histology and ultrasound investigations.

A pilomatricoma was considered “atypical” if at least 3 out of 4 dermatologists disagreed on the diagnosis of pilomatricoma. Two groups were therefore created: lesions that were suspected of being pilomatricomas, and lesions that were not. In the latter cases, other differential diagnoses were suggested.

We identified all the studies indexed in PubMed until 31 July 2023. All papers reported in the present study were based on clinical studies involving humans, including case reports, case series and reviews. The search parameters included the terms “pilomatricoma in children”, “dermoscopic findings in pilomatricoma”, “typical dermoscopy of pilomatricoma”, “atypical dermoscopy of pilomatricoma” and “pilomatricoma dermoscopy”. A subsequent review of the respective bibliographies aimed to identify any undetected reports. Apart from two articles in German and French, only papers written in English were considered in the review.

Results

We observed and studied 55 children with pilomatricomas. Results are summarized in Table 2.

Females were involved in 60% of cases. Mean age was 7 years. Two patients presented with 2 pilomatricomas without extracutaneous manifestations, leading to the identification of 58 pilomatricomas in our retrospective analysis.

Thirty-eight of 58 (65%) pilomatricomas were located on the head-neck region, 14 (24%) on the upper limbs and a few cases on the lower limbs, back and abdomen.

Clinically, pilomatricomas typically present as pigmented nodules. Forty-six pilomatricomas in our case series (79%) exhibited single or multiple colors ranging from blue to red or yellow (Figure 1, A, C and E). The nodules were exophytic, ulcerated, or subcutaneous in 17.2% of cases (Figure 1G). The mean diameter of the lesions was 7 mm.

Furthermore, rare clinical types of pilomatricomas characterized by anetodermic or keloid-like appearance were described (3% of cases).

An ultrasound scan was prescribed for 24 children (44%) and the report included the following features: dimensions,
Table 1. Overview of the Literature Review.

<table>
<thead>
<tr>
<th>Study and Year of Publication</th>
<th>Type of Study</th>
<th>N. of Patients Involved With Dermoscopy Aviable</th>
<th>Case N.</th>
<th>Age and Sex</th>
<th>Cutaneous Area Involved</th>
<th>Typical at Dermoscopy</th>
<th>Atypical at Dermoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedro Zaballos et al, 2008 [3]</td>
<td>Clinical study</td>
<td>10</td>
<td>1</td>
<td>75, F</td>
<td>Arm</td>
<td>Tricolor pathognomonic appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>40, M</td>
<td>Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>45, M</td>
<td>Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>12, F</td>
<td>Face</td>
<td>Tricolor pathognomonic appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>36, F</td>
<td>Neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>52, F</td>
<td>Face</td>
<td>Tricolor pathognomonic appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>16, M</td>
<td>Face</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>18, F</td>
<td>Arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>14, F</td>
<td>Face</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>60, F</td>
<td>Face</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivette Alarcon et al, 2014 [6]</td>
<td>Case report</td>
<td>1</td>
<td>1</td>
<td>12, M</td>
<td>Left cheek</td>
<td>Tricolor pathognomonic appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>48, M</td>
<td>Left eyebrow</td>
<td>Nodular bicolor appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>58, M</td>
<td>Left side of the nose</td>
<td>Nodular bicolor appearance</td>
<td></td>
</tr>
<tr>
<td>Wolf et al, 2014 [8]</td>
<td>Case report</td>
<td>1</td>
<td>1</td>
<td>4, M</td>
<td>Left cheek</td>
<td>Nodular pilomatricoma with blue-red color mimicking vascular lesion</td>
<td></td>
</tr>
<tr>
<td>Chen et al, 2020 [9]</td>
<td>Case report</td>
<td>1</td>
<td>1</td>
<td>14, M</td>
<td>Left arm</td>
<td>Nodular bicolor appearance</td>
<td></td>
</tr>
<tr>
<td>Neema et al. 2022 [10]</td>
<td>Case report</td>
<td>2</td>
<td>1</td>
<td>34, F</td>
<td>Left cheek</td>
<td>Tricolor pathognomonic appearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>42, F</td>
<td>Right pinna</td>
<td>Tricolor pathognomonic appearance</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 continues
Table 1. Overview of the Literature Review. (continued)

<table>
<thead>
<tr>
<th>Study and Year of Publication</th>
<th>Type of Study</th>
<th>Patients</th>
<th>N. of Patients Involved With Dermoscopy Aviable</th>
<th>Case N.</th>
<th>Age and Sex</th>
<th>Cutaneous Area Involved</th>
<th>Typical at Dermoscopy</th>
<th>Atypical at Dermoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>42, M</td>
<td>Left mammary area</td>
<td></td>
<td>Anetodermic pilomatricoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>70, F</td>
<td>Left forehead region</td>
<td></td>
<td>Anetodermic pilomatricoma</td>
</tr>
<tr>
<td>Fink et al, 2017 [12]</td>
<td>Case report</td>
<td>1</td>
<td></td>
<td>1</td>
<td>3, M</td>
<td>Right zygomatic arch</td>
<td></td>
<td>Molluscum-like appearance</td>
</tr>
<tr>
<td>Huet et al, 2018 [13]</td>
<td>Case report</td>
<td>1</td>
<td></td>
<td>1</td>
<td>10, M</td>
<td>Left temporal region</td>
<td></td>
<td>Tricolor pathognomonic appearance</td>
</tr>
</tbody>
</table>

Among them, 4 pilomatricomas (33%) presented as small nodules with a central white-yellowish component, surrounded either by an erythematous (red) halo or by crown vessels. In these cases, a dermoscopic diagnosis of molluscum contagiosum was proposed (Figure 2, A and B). In 4 cases (33%), pilomatricomas presented as subcutaneous nodules with a red or blue background and arborizing-like or reticular pattern linear-irregular flat vessels, mimicking calcified vascular lesions (Figure 2, C and D). Two pilomatricomas (17%) resembled melanocytic lesions showing a brown pseudonetwork or homogeneous blue pattern at dermoscopy (Figure 2, E and F). In 2 cases (17%) the clinical presentation was keloid-like. Furthermore, biopsy of a lesion was performed to exclude a possible malignancy such as dermatofibrosarcoma protuberans (Figure 2, G and H).

Histological examination revealed a relatively well-circumscribed, dermal or dermal-subcutaneous, multilobulated tumor, surrounded by a variable connective tissue stroma. The tumor consisted of islands of cells in a circular distribution with anucleated shadow cells in the center and basophilic cells in the periphery.

In addition, certain distinctive histological characteristics may be associated with the particular clinical-dermoscopic variant. Tricolor pilomatricomas, for example, showed calcifications or melanin pigment in the lobules (Figure 3A). Dilated blood vessels overlying the tumor were observed in the vascular type (Figure 3B). Keloid-like pilomatricomas, on the other hand, featured a loss of collagen and elastic fibers in the superficial dermis overlying the lesion. Dermoscopichistopathological correlation showed that bluish areas were associated with the presence of melanin pigment, white areas...
localized on the head-neck region [14]. Multiple pilomatricomas may be associated with myotonic dystrophy, familial adenomatous polyposis-related syndromes (including Gardner syndrome), Turner syndrome, or Rubinstein-Taybi syndrome [15,16]. Ciricaks Ket al found that the presence of six or more pilomatricomas is highly suggestive for an underlying syndrome (>95% specificity), so these patients should undergo additional screening [15]. In our retrospective analysis, two children presented with multiple pilomatricomas but further investigations were negative.

Pilomatricomas may present with a varied morphology, therefore, making preoperative diagnosis challenging. The literature highlights an exophytic pigmented lesion as the

with calcification, red areas with dilated blood vessels and white streaks corresponded to fibrosis on histopathology.

Conclusions

According to our study and the review of the literature, pilomatricoma is more common in females and it is mainly
Dermoscopy may be a useful tool in order to improve the detection of pilomatricomas. In the largest case series described by Zaballos et al, the use of dermoscopy increased the diagnostic sensitivity for pilomatricoma from 50% to 90% [3]. On the other hand, in our retrospective analysis, clinical and dermoscopic features were suspicious or suggestive of pilomatricoma in only 79% of children, while in 21% of cases, they were insufficient to make the diagnosis and histology was required. Zaballos et al reported the presence of multiple irregular whitish structures and streaks on dermoscopy in 90% of cases [3]. In contrast, in our retrospective study, yellow/whitish areas were found only in 50% of pilomatricomas. These differences in sensitivity and dermoscopic findings may be related to the larger and different sample size (55 pediatric patients included in our analysis versus only 3 children described by Zaballos et al).

The systematic review of the literature highlighted that both cases of typical and atypical pilomatricomas have been reported.

The tricolor appearance could be considered as a dermoscopic clue to make the diagnosis. In this regard, several authors reported typical pilomatricomas characterized by a bi- or tricolor nodular aspect at dermoscopy [3-6,9,10,13]. In contrast, dermoscopy of atypical pilomatricoma has rarely been reported in the literature [7,8,11,13-15]. Several authors have described nodules characterized by yellowish lobules on an erythematous background, surrounded by crown-like branching vessels features that can also be found in molluscum contagiosum, which must be considered as a differential diagnosis [7,13].

Wolff et al reported a 4-year-old boy with a red-blue nodule, 0.5 cm in diameter, characterized by a homogeneous blue-red color and linear white structures on non-polarized dermoscopy. Histology was required to exclude a calcified hemangioma. In addition, Dev et al reported three cases of anetodermic pilomatricoma, which is extremely rare and presents clinically with a scar-like appearance [11,15]. Dermoscopy is inconclusive in these cases and dermoscopic-histopathological correlation is essential to differentiate between dermatofibroma and dermofibrosarcoma protuberans [15].

Clinical and dermoscopic findings of pilomatricoma in pediatric age are poorly reported in the literature.

Our large case series and systematic review of the literature indicate that in approximately 80% of cases dermoscopy may be sufficient to diagnose or suspect pilomatricoma, whereas in the remaining 20% of cases histological examination is necessary to confirm the diagnosis and exclude malignancy of the lesion.

**Figure 2.** (A,B) Shiny papulo-nodular lesion localized on the face of a 9-year-old child showing homogeneous yellow-white central area with crown vessels at dermoscopy. (C,D) Subcutaneous red nodule on the malar region of a 12-year-old child characterized by large linear-irregular vessels on yellow-whitish background at dermoscopy. (E,F) Flat blue lesion localized on the neck of a 11-year-old child, dermoscopy shows light blue homogeneous areas. (G,H) Plaque irregular in shape 1.5cm diameter nodule, localized on the back of a 8-year-old child, dermoscopy shows an unspecific red homogeneous pattern with unfocused vessels.

typical and suggestive presentation of pilomatricoma in the pediatric population. Such lesions can be ulcerated or non-ulcerated and may exhibit variable pigmentation with combinations of blue-gray, red, and white/yellow colors [4,6-8,10,12-14]. Additionally, atypical pilomatricomas with an anetodermic appearance have also been reported [5,9,11]. In the literature, ultrasound was used to confirm, support or exclude the diagnosis of pilomatricoma [18,19]. Once the diagnosis has been confirmed, surgical excision may be considered for aesthetic and functional reasons.
Figure 3. (A) Tricolor type pilomatricoma: peripheral aggregates of basaloid cells and central large masses of eosinophilic cornified material containing shadow cells. Calcification (yellow circles) and melanin pigment (green arrows) are present into the lobules (H&E, ×60). (B) Tricolor type pilomatricoma (H&E, ×90). (C) Vascular type of pilomatricoma: non-capulated tumor proliferation in the central area of the dermis, with basaloid cells (blue circle) with an abrupt transition to shadow cells (green circle), dilated vessels between the tumor and the epidermis (red arrows) (H&E, ×90).

References

15. Mesa-Álvarez L, Batalla A, Iglesias-Pazas Á, Álvarez C, Flórez Á. Multiple Pilomatricomas: A Retrospective Study and Literature


To the Editor,

Current approaches to specialized dermatologic care for patients across sexes, gender identities, and sexual orientations are hindered by notable deficiencies in educational experiences for rising medical residents and attendings, which poses significant challenges for this population. It is crucial to address these shortcomings both comprehensively and compassionately. Creating equitable, inclusive, and culturally sensitive care environments is paramount to ensuring that all individuals may seek help without fear of judgment or discrimination.

In cisgendered male and female patients, discrepancies across genital dermatosis diagnoses have been partially attributed to patient preferences and dermatology residents’ clinical experiences. In a cross-sectional multicenter study of 729 participants analyzing gender differences in diagnosing genital lichen sclerosus (LS), women were more likely than men to obtain a referral with a correct suspected diagnosis of LS prior to diagnosis at the referral center (62.8% vs. 54.8%, respectively, \( P=0.003 \)) [1]. Women more frequently reported severe symptoms (visual analogue scale score 6/10 or more) compared to men, including itching (39.0% vs. 11.0%, \( P<0.001 \)), burning (31.6% vs. 9.9%, \( P<0.001 \)), and dyspareunia (35.8% vs. 15.6%, \( P<0.001 \)) [1].

Currently, there is a paucity of clinical experience in genital dermatology in the majority of medical schools, residency programs, and fellowships [2]. Male and female dermatology residents exhibit differing approaches to the treatment of conditions such as genital LS. These differences might be because patients commonly prefer physicians of their same gender for anogenital examinations, forming potential bias in experience [2]. A survey-based study \( (n=110) \) reported that male residents \( (n=45) \) exhibited lower comfort levels in performing female genitalia examinations compared to female residents \( (n=65; \ P=0.001) \). Similarly, female residents reported lower comfort levels for performing male genital...
examinations compared to male residents (P<0.001) [3]. In this same study, on average, PGY-4 dermatology residents (n=31) reported greater confidence in treating and counseling genital LS patients compared to PGY-2 residents (n=32) [3], underscoring the importance of education and case exposure for improved care. Additionally, in a 2020 survey of dermatology residents (n=95) on preferences for learning about LS, residents reported the lowest preference for in-person experiences with an LS expert (10%), compared to learning from lectures (24%), journal articles (19%), book chapters (18%), and peer discussions (17%) [4]. Moreover, the majority of residents reported never showing patients the exact location to apply topical medications, with a smaller proportion of male residents doing so compared to female residents (25% [10/40] and 42% [23/55], respectively, P=0.004) [4].

Individuals identifying with the LGBTQIA+ community require substantial and complex dermatologic care, including both physical (e.g., genital dermatology and/or hirsutism) and psychosocial needs [4]. Transgender patients, especially, rely on dermatologist support during their transition process for a range of aesthetic and medical treatments [5]. However, patient fears of stigmatization and negative prior experiences with the health care system may hinder them from seeking medical care [6]. For example, in a survey-based study analyzing first-year medical students’ attitudes towards homosexual men and women among medical students, 45.79% of the 2,088 heterosexual first-year medical student respondents reported explicit bias and 81.51% reported implicit bias against homosexual individuals [7]. Currently, education on LGBTQIA+ content is limited within the medical school curricula, leaving many graduates uncomfortable with caring for LGBTQIA+ patients. A 2012 survey-based study reported that 52% of the responding faculty from U.S. medical education institutions had no formal LGBTQIA+ competency training (N=69; P<0.05) [6, 8]. Inadequate care or lack of access to desired procedures may result in illicit procedures, which may cause significant morbidity or mortality. For transgender women, injected substances have included industrial-grade silicone and automobile transmission fluid, causing serious complications, temporary or permanent injuries, and death [9].

Mitigating the complications that may arise from inexperienced or limited access to care requires adaptations that encompass education and awareness. The quality of patient care may substantially benefit from greater clinical exposure to a spectrum of genders and sexualities during residency training. Openness to new practices and experiences may support easier assimilation into proper, adaptive care for these individuals. Future directions include increased collaboration with LGBTQIA+ organizations, cultural competency training, and reassessment of curriculum inclusiveness.

References
Disparities in Financial Burden, Outcomes, and Comorbidities Among Pediatric Patients With Pyoderma Gangrenosum With and Without Mental Health Disorders in a Multivariate Analysis of the 2016 Kids’ Inpatient Database

Amar D. Desai¹, Angela Lu², Faraz Yousefian³, Shari R. Lipner⁴

¹ Rutgers New Jersey Medical School, Newark, NJ, USA
² Albert Einstein Medical School, Bronx, NY, USA
³ Center for Clinical and Cosmetic Research, Aventura, FL, USA
⁴ Weill Cornell Medicine, Department of Dermatology, New York, NY, USA

Key words: pyoderma gangrenosum, mental health, pediatric, management, outcomes

Citation: Desai AD, Lu A, Yousefian F, Lipner SR. Disparities in Financial Burden, Outcomes, and Comorbidities Among Pediatric Patients With Pyoderma Gangrenosum With and Without Mental Health Disorders in a Multivariate Analysis of the 2016 Kids’ Inpatient Database. Dermatol Pract Concept. 2024;14(2):e2024057. DOI: https://doi.org/10.5826/dpc.1402a57

Accepted: November 1, 2023; Published: April 2024

Copyright: ©2024 Desai et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: Mr. Desai, Ms. Lu, and Dr. Yousefian have no conflicts of interest. Dr. Lipner has served as a consultant for Ortho-Dermatologics, BelleTorus Corporation, Moberg Pharmaceuticals, and Hoth Therapeutics.

Authorship: All authors have contributed significantly to this publication. Amar D. Desai and Angela Lu should be considered as joint co-first author.

Corresponding Author: Shari R. Lipner Weill Cornell Medicine, Department of Dermatology, New York, NY, USA.
Email: shl9032@med.cornell.edu

Introduction

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis, with painful and rapidly progressing skin ulcers [1]. An association between PG and mental, behavioral, and neurodevelopmental disorders (MBNDs), including depression, has been described in adult patients [2] but has not been studied in pediatric or inpatient populations. We aimed to assess differences in demographics, severity of disease, comorbidities, and outcomes in pediatric inpatients with PG with and without MBNDs.

The 2016 Kids’ Inpatient Database (KID), a database on hospital stays for children ages 0–20 years old, was queried for patients with PG (ICD10-CM: L88) with and without MBNDs (ICD-10: F01-F99). Univariate analysis with Chi-square and two-tailed t-test statistics, alpha-value of 0.05, and multivariable analysis were performed to identify statistical associations with MBNDs.

A total of 107 pediatric inpatients were diagnosed with PG, with mean age 15.6 years (SE: 0.5), 70.8% female, 46.8% White, and 26.6% Black. Age, race, household...
Research Letter | Dermatol Pract Concept. 2024;14(2):e2024057

income, and severity of illness varied with MBND status (P<0.05). PG patients with vs. without MBNDs more often had Crohn's disease or ulcerative colitis (87.5% vs. 48.2%, P<0.001), musculoskeletal and connective tissue disease (45.8% vs. 21.7%), and were overweight or obese (33.3% vs. 13.3%, P=0.023). On multivariable analyses, patients with vs. without MBNDs had greater total charges ($153,022 vs. $90,506, P=0.019), length of stay (21.5 vs. 8.3 days, P=0.001), and number of procedures performed (5.7 vs. 2.6, P=0.001) (Table 1).

### Table 1: Demographics, management, charges, and outcomes of pediatric patients with pyoderma gangrenosum by mental health diagnosis status.

<table>
<thead>
<tr>
<th></th>
<th>No Mental Health Diagnosis</th>
<th>Mental Health Diagnosis</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 83</td>
<td>n = 24</td>
<td>n = 107</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−77.7%</td>
<td>−22.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean [SE])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.05</td>
<td>17.37</td>
<td>15.57</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>[0.61]</td>
<td>[0.37]</td>
<td>[0.49]</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31.30%</td>
<td>21.70%</td>
<td>29.20%</td>
<td>0.371</td>
</tr>
<tr>
<td></td>
<td>[15.44]</td>
<td>[12.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>68.70%</td>
<td>78.30%</td>
<td>70.80%</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41.70%</td>
<td>63.60%</td>
<td>46.80%</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>[5.68]</td>
<td>[11.58]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34.70%</td>
<td>0.00%</td>
<td>26.60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[12.11]</td>
<td>[0.000]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.30%</td>
<td>18.20%</td>
<td>16.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[11.47]</td>
<td>[10.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.30%</td>
<td>18.20%</td>
<td>10.60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.00]</td>
<td>[10.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary payer status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medicare</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>1.20%</td>
<td>0.00%</td>
<td>0.90%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.00]</td>
<td>[0.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medicaid</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>34.10%</td>
<td>33.30%</td>
<td>34.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[19.79]</td>
<td>[17.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Private insurance</td>
<td></td>
<td></td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>59.80%</td>
<td>45.80%</td>
<td>56.60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[17.87]</td>
<td>[18.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-pay</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>3.70%</td>
<td>8.30%</td>
<td>4.70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.00]</td>
<td>[1.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>1.20%</td>
<td>12.50%</td>
<td>3.80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.00]</td>
<td>[4.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crohn's disease or ulcerative colitis</td>
<td>48.20%</td>
<td>87.50%</td>
<td>57.00%</td>
</tr>
<tr>
<td></td>
<td>[26.00]</td>
<td>[65.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous infections</td>
<td>38.60%</td>
<td>17.40%</td>
<td>34.00%</td>
</tr>
<tr>
<td></td>
<td>[15.40]</td>
<td>[9.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal &amp; connective disease</td>
<td>21.70%</td>
<td>45.80%</td>
<td>27.10%</td>
</tr>
<tr>
<td></td>
<td>[11.01]</td>
<td>[25.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overweight and obesity</td>
<td></td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>13.30%</td>
<td>33.30%</td>
<td>17.80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[8.01]</td>
<td>[16.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertensive disease</td>
<td></td>
<td></td>
<td>0.547</td>
</tr>
<tr>
<td></td>
<td>8.40%</td>
<td>12.50%</td>
<td>9.30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[6.00]</td>
<td>[10.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td>0.141</td>
</tr>
<tr>
<td></td>
<td>8.40%</td>
<td>0.00%</td>
<td>6.50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[6.00]</td>
<td>[0.000]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermatitis &amp; eczema</td>
<td></td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>1.20%</td>
<td>12.50%</td>
<td>3.80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.00]</td>
<td>[4.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Charges</td>
<td></td>
<td></td>
<td>0.289</td>
</tr>
<tr>
<td></td>
<td>Charges (US$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean [SE])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90,505.94</td>
<td>153,051.59</td>
<td>104,288.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[15,166.55]</td>
<td>[55,634.25]</td>
<td>[17,065.09]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of stay</td>
<td></td>
<td></td>
<td>0.207</td>
</tr>
<tr>
<td></td>
<td>Number of days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean [SE])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.27</td>
<td>21.48</td>
<td>11.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1.08]</td>
<td>[10.12]</td>
<td>[2.43]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of procedures</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>(mean [SE])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>5.73</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.31]</td>
<td>[1.15]</td>
<td>[0.37]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time until 1st procedure</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Number of days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean [SE])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.27</td>
<td>11.98</td>
<td>4.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.30]</td>
<td>[6.41]</td>
<td>[1.48]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td></td>
<td></td>
<td>0.345</td>
</tr>
<tr>
<td></td>
<td>Mortality rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.60%</td>
<td>0.00%</td>
<td>2.80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1.79]</td>
<td>[0.000]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>Complication rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16.90%</td>
<td>21.70%</td>
<td>17.90%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[9.79]</td>
<td>[12.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td></td>
<td></td>
<td>0.345</td>
</tr>
<tr>
<td></td>
<td>Complication rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.60%</td>
<td>0.00%</td>
<td>2.80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1.79]</td>
<td>[0.000]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute kidney failure</td>
<td></td>
<td></td>
<td>0.512</td>
</tr>
<tr>
<td></td>
<td>Complication rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.40%</td>
<td>4.30%</td>
<td>7.50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[5.30]</td>
<td>[2.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI bypass of ileum</td>
<td></td>
<td></td>
<td>0.335</td>
</tr>
<tr>
<td></td>
<td>Procedure rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.60%</td>
<td>8.30%</td>
<td>4.70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[1.79]</td>
<td>[3.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI excision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procedure rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.50%</td>
<td>47.80%</td>
<td>21.70%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>[5.30]</td>
<td>[15.30]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case Presentation

We found that pediatric PG patients with vs. without MBNDs had greater physical and financial burden. Similarly, in a 2002–2012 National Inpatient Sample (NIS) retrospective study of 7,569 adult PG inpatients, those with vs. without MBNDs had 30% greater inpatient mortality rates and $9 million greater hospitalization costs annually [3].

In our study, PG patients with MBNDs had almost twice the prevalence of Crohn’s disease or ulcerative colitis than PG patients without MBNDs. In a retrospective study of 259 PG patients from German dermatologic wound care centers, 25.8% had ulcerative colitis, 10.6% had Crohn’s disease, 22.5% had GI disorders, 69.5% had diabetes mellitus, and 36.7% had another endocrine disorder, with the presence of multiple comorbidities being associated with more severe PG [4]. Therefore, our study and others highlight the connection between PG and MBNDs as well as consideration of the mental health status of PG patients, which may impact overall health outcomes [5].

KID may not be representative of all United States pediatric PG patients. The study was limited to inpatient data and did not include outpatient data. Cases were retrospectively reported without dermatologist or psychiatrist confirmation, clinical examination, or treatment information, limiting our analysis.

Conclusion

We conclude that pediatric PG patients with vs. without MBNDs have significant disparities in financial burden, hospitalization outcomes, and comorbidities. Therefore, we recommend screening PG patients for MBNDs. We advocate for a multidisciplinary collaboration between dermatologists and psychiatrists to provide mental and behavioral support to PG patients with MBNDs, which may improve patient quality of life and reduce health care costs [6].

References

Acral Arteriovenous Hemangioma: A Case Report and the Utility of Ultra-High Frequency Ultrasound (UHFUS) in Diagnosis

Stefania Guida1,2, Antonio Podo Brunetti1, Gianmarco Diego Bigotto1, Giorgio Stabile1, Franco Rongioletti1,2

1 Vita-Salute San Raffaele University, Milan, Italy
2 Dermatology Clinic, IRCCS San Raffaele Scientific Institute, Milan, Italy

Key words: acral arteriovenous hemangioma, arteriovenous tumor, ultra-high frequency ultrasound, vascular tumor


Accepted: October 10, 2023; Published: April 2024

Copyright: ©2024 Guida et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Antonio Podo Brunetti, MD, Vita-Salute San Raffaele University, Via Olgettina, 58 20132, Milan, Italy. E-mail: a.podobrunetti@gmail.com

Introduction

Acral arteriovenous hemangioma is a rare vascular lesion with an uncertain etiology predominantly affecting middle-aged adults. The lesion typically manifests as a painless 0.5–1 cm erythematous-violaceous papule, predominantly affecting the face and extremities [1]. We present a case study of a middle-aged female diagnosed with acral arteriovenous hemangioma of the lower lip. The clinical, histological, dermoscopic, and immunohistochemical features of this condition are discussed, highlighting the importance of a multidimensional diagnostic approach. Additionally, the application of ultra-high frequency ultrasound (UHFUS) with color Doppler as a diagnostic tool is introduced.

Case Presentation

A 53-year-old female presented with an asymptomatic persistent lower lip edema that had been present for four months. Previous episodes of transient and self-resolving lower lip swelling were referred. Clinical evaluation revealed swelling of the lower lip (Figure 1A). Dermatoscopy showed non-specific vascular congestion with non-arborising telangiectasia in the absence of lacunae (Figure 1B). Several differential diagnoses, including Miescher’s granulomatous cheilitis,
infectious causes, and neoplastic conditions, were considered. Skin biopsy revealed a benign dermal vascular proliferation characterized by thick-walled blood vessels containing muscle and lined with a single layer of endothelial cells intermingled with thin-walled dilated blood vessels (Figure 1C). Immunohistochemistry showed positive CD34 staining, further supporting the vascular nature of the lesion. Additionally, focal positivity for WT-1 and negativity for D2-40 aided in distinguishing this vascular entity from other vascular or lymphatic tumors and malformations (Figure 1D,E,F).

**Conclusion**

The exact nature of arteriovenous tumors remains uncertain; however, the prevailing hypothesis proposes a multicentric hamartomatous origin from the suprapapillary vascular plexus with arteriovenous anastomoses. Its clinical diagnosis can be challenging, with accurate identification achieved in less than 5% of cases [4]. Dermoscopy has emerged as a valuable tool in the diagnosis of arteriovenous tumors exhibiting a pattern including non-arborising telangiectasia on a reddish background and the absence of lacunae in 72% of cases [5]. However, despite its utility, dermoscopy has inherent limitations that hinder the assessment of each structure or pattern’s specificity in diagnosing arteriovenous tumors, and histopathological evaluation continues to serve as the definitive gold standard for diagnosis. This case highlights the rarity of acral arteriovenous hemangioma and emphasizes...
the importance of integrating clinical, histological, immunohistochemical, and imaging data for an accurate diagnosis. Additionally, the potential application of UHFUS with color Doppler as a diagnostic tool for this vascular entity is proposed.

References

Dermoscopic Evaluation of Combined Treatment with Fractional Co2 and Nanosecond Q-1064 nm Laser for Traumatic Facial Tattoo

Claudio Conforti1, Piergiorgio Turco2, Sebastian Laspina3, Domenico Piccolo4, Vito Cazzato5

1 IDI-IRCCS, Dermatological Research Hospital, Rome, Italy
2 Department of Plastic and Reconstructive Surgery, University of Naples Federico II, Naples, Italy
3 Private Practice, Centrolaser Laspina, Udine, Italy
4 Skin Center-Dermo Aesthetic Laser Centers, Avezzano, Italy
5 Department of Plastic and Reconstructive Surgery, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste University Hospital, Trieste, Italy

Key words: laser, dermoscopy, tattoo

Citation: Conforti C, Turco P, Laspina S, Piccolo D, Cazzato V. Dermoscopic Evaluation of Combined Treatment With Fractional Co2 and Nanosecond Q-1064 nm Laser for Traumatic Facial Tattoo. Dermatol Pract Concept. 2024;14(2):e2024087. DOI: https://doi.org/10.5826/dpc.1402a87

Accepted: October 1, 2023; Published: April 2024

Copyright: ©2024 Conforti et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Claudio Conforti, MD, IDI-IRCCS, Dermatological Research Hospital, 00167 Rome, Italy. E-mail: claudioconforti@yahoo.com

Introduction

Traumatic facial tattoos are a disabling sequel altering the person’s appearance. They are caused by the depositing of exogenous pigmented particles during a traumatic event into the dermis. The effectiveness of nanosecond Q-1064 nm has been proven to be an effective procedure to treat this condition, and nowadays it is the first-line option [1], but recently, with the aim to improve the aesthetic outcome of the scars caused by the trauma as well, some authors have successfully combined the use of the CO2 ablative fractional laser (AFL) with the nanosecond Q-1064 nm laser [2]. However, little is known about the dermatoscopic changes that combined laser treatment brings to tissue with traumatic tattoo. Herein, we report one case of upper labial traumatic tattoo (black-blue color) treated with combined use of nanosecond Q-1064 nm and AFL laser; after each laser session, we performed a dermatoscopic analysis on the tissue. Each dermatoscopic change has been accurately reported and described.

Case Presentation

An otherwise healthy 26-year-old female who, after a bicycle fall with impact of her face on the asphalt, sustained an injury to the left upper prolabium, resulting in a 12 x 4 mm black pigmented scar located in the upper left labial region (Figure 1a). First, a dermatoscopic evaluation was performed in order to choose the best laser treatment. Dermoscopically, a white structureless area surrounded by a bluish pigmentation...
was observed. The white area corresponded to the scar, while the bluish color corresponded to the presence of small particles of asphalt in the dermis. In order to treat the scar and to bring out the exogenous pigmented particles, a first session of nanosecond Q-1064 nm laser treatment was performed, followed by a fractional CO2 laser treatment. Immediately after the procedure, dermoscopic evaluation was performed, which observed the absence of asphalt particles, the presence of laser-induced channels through which the pigment was removed, and mild erythema around the treatment area as a consequence of the two lasers treatment performed.

After three months of follow-up, the clinical result was a eutrophic scar with good quality texture and without any pigment; the dermatoscopic exam confirmed the clinical result without presence of residual exogenous pigment.

Conclusion

Tattoo removal and scarring improvement are the two endpoints for traumatic scarring tattoo treatment [1]. Our experience shows that Q-1064 nm laser can penetrate in skin tissues and fragments the asphalt particles into smaller units. In this condition, fractional CO2 laser creates channels which allow the pigmented particles to escape. The combined protocol optimizes the effectiveness of the treatment. According to our experience, combined laser treatment with CO2 AFl, and Q-1064 nm laser could facilitate the treatment of asphalt scars, allowing effective removal of the pigment particles and at the same time improving the texture of the scar, as demonstrated by dermatoscopic evaluation.

References

Dermoscopic Presentation of Two Cases of Pigmented Purpuric Dermatosis-like Mycosis Fungoides

Neil Vaishampayan¹, Andrew Schuler², Anne Ning², Alexandra Hristov², Douglas Fullen², Trilokraj Tejasvi²

¹ University of Michigan Medical School, Ann Arbor, Michigan, USA
² Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA

Key words: dermoscopy, purpuric mycosis fungoides, PPD

Introduction

Purpuric mycosis fungoides (PMF) is an extremely rare subtype of cutaneous T-cell lymphoma. The diagnosis of PMF is often challenging as its clinical presentation and dermoscopy findings closely resemble pigmented purpuric dermatosis (PPD) [1]. Given the low incidence of PMF, there is a paucity of literature concerning the dermoscopic findings of this entity. A case series by Nasimi et al. compared the dermoscopy features of 28 cases of PMF and 13 cases of PPD. The presence of spermatozoa-like structures and fine short linear vessels were found to be statistically significant distinguishing features of PMF on dermoscopy [1]. Additionally, dermoscopy findings of erythematous clods on a coppery background and reticular pigmentation were significantly associated with PPD compared to PMF [1-3]. Here, we showcase two cases of histopathology-confirmed PMF that did not display the specific dermoscopy features of PMF previously described in the literature. Instead, our dermoscopy findings more closely resembled classic findings seen in benign PPD, representing a potential diagnostic pitfall.

Case Presentation

Case 1. An otherwise healthy 13-year-old presented with a 5-year history of stable asymptomatic red-brown patches affecting the groin, buttocks, thighs, and upper inner arms. Clinical examination revealed cayenne-pepper-colored patches and macules. Dermoscopy displayed dotted and clustered vessel morphology and distribution, no scales, no follicular findings, erythematous clods with interspersed brown dots, and admixed brown reticular lines on a coppery-brown background [4]. Histopathology revealed
an atypical CD3+/CD8+ lymphoid infiltrate showing epi-
dermatropism loss of CD7 and diminished CD5. Erythema-
tous clods, seen on dermoscopy, corresponded to numerous
extravasated erythrocytes. T-cell clonality studies demon-
strated a clonal T-cell population. This constellation of find-
ings indicated PMF.

Case 2. A 65-year-old female with history of a B-cell
lymphoproliferative disorder and biopsy-confirmed mycosis
fungoides on her left abdomen presented with pruritic
flare of a poorly demarcated eryhematous rash with
cayenne-pepper macules, notably on her left calf. Dermos-
copy showed dotted vessel morphology, no scales, no follic-
ular findings, and red clods with interspersed brown dots on
a coppery-brown background [4]. Histopathology revealed
a CD4-positive, epidermotropic T-cell infiltrate with loss
of CD7 and extravasation of erythrocytes. T-cell clonality
studies showed a clonal T-cell population with base pair
peaks identical to the abdomen. The patient was diagnosed
with PMF.

Conclusion
The dermoscopic findings in these cases of PMF are distinct
from findings in the literature. Notably, our cases lacked
spermatozoa-like structures and fine short linear vessels, which
have been associated with conventional mycosis fungoides
(MF) as well as with PMF [1, 5]. The dermoscopic findings
in our cases were more in keeping with conventional PPD [5].
Furthermore, there is a wide spectrum of dermoscopic features
associated with mycosis fungoides ranging from linear vessels
and white scales to the red-brown globules, no scales, and
brown reticular lines described in these cases. Indeed, the wide
range of reported dermoscopic features within MF render diag-
nosis based on dermoscopy alone challenging [6]. Further study
is needed to adequately describe the dermoscopic features of
PMF and differentiate it from potential mimickers. In lieu of
reliable dermoscopic features in PMF, it is imperative that the
clinician integrates clinical, dermoscopic, and ancillary studies
and histologic features for correct diagnosis.

Figure 1. PMF (Case 1): A) Clinical: 13-year-old with cayenne-pepper-colored patches and macules
on thighs and groin. B) Dermoscopy: erythematos globules, interspersed brown dots, admixed
brown reticular lines on a coppery-brown background. C) Histopathology: Epidermotropic and
band-like lymphocytes with numerous extravasated erythrocytes.
Table 1. Existing dermoscopy findings of PMF and PPD in the literature compared to our two reported cases [1, 2, 5].

<table>
<thead>
<tr>
<th>PMF</th>
<th>PPD</th>
<th>Two reported cases of PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spermatozoa-like vascular morphologic structures</td>
<td>Erythematous globules</td>
<td>Erythematous clods with interspersed brown dots</td>
</tr>
<tr>
<td>Fine short linear vessels</td>
<td>Reticular pigmentation</td>
<td>Admixed brown reticular pigmentation lines</td>
</tr>
<tr>
<td>Orange-yellow background</td>
<td>Dull red-brown background</td>
<td>Coppery-brown background</td>
</tr>
<tr>
<td>Distributed dotted vascular morphology</td>
<td>Distributed dotted vascular morphology</td>
<td>Dotted vascular morphology</td>
</tr>
<tr>
<td>Clustered vascular distribution</td>
<td>Clustered vascular distribution</td>
<td>Clustered vascular distribution</td>
</tr>
<tr>
<td>No scales</td>
<td>No scales</td>
<td>No scales</td>
</tr>
</tbody>
</table>

In boldface: Features described as statistically significant for the condition in the existing literature.


Parental Preferences Regarding the Novel Systemic Treatment for Atopic Dermatitis in Children

Alicja Mesjasz1, Monika Suszyńska2, Marta Jaskulak3, Magdalena Trzeciak4

1 Dermatological Students Scientific Association, Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland
2 Department of Radiology, Faculty of Medicine, Regional Specialized Children’s Hospital in Olsztyn, Olsztyn, Poland
3 Department of Immunobiology and Environmental Microbiology, Faculty of Health Sciences, Medical University of Gdansk, Gdansk, Poland
4 Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland

Key words: atopic dermatitis, monoclonal antibodies, dupilumab, Janus kinase inhibitors

Citation: Mesjasz A, Suszyńska M, Jaskulak M, Trzeciak M. Parental Preferences Regarding the Novel Systemic Treatment for Atopic Dermatitis in Children. Dermatol Pract Concept. 2024;14(2):e2024108. DOI: https://doi.org/10.5826/dpc.1402a108

Accepted: November 29, 2023; Published: April 2024

Copyright: ©2024 Mesjasz et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Prof. Magdalena Trzeciak M.D., PhD, Department of Dermatology, Venereology and Allergology, Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland, tel: +48-501 188 586 Email: mtrzeciak@gumed.edu.pl

Introduction

Atopic dermatitis (AD) is a dermatosis that affects up to 20% of children and 3-7% of adults globally [1].

Over the past few years, several biologics and inhibitors of Janus kinases (JAKi) have been approved for the treatment of moderate to severe AD [2].

Very little study has been conducted on the tendencies of patients towards characteristics of novel therapies, with even fewer exploring the preferences of parents [2].

Case Presentation

A total of 221 participants were included in the study. They have the option to select from the alternatives provided in Table 1. The majority of respondents (80.09%) were aged between 21-40. The average age of the patient was 4.67 years.

The average Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD) was 45.48288 ±19.81465.

Up to 73.76% of parents would choose medication taken every day in a tablet form over an every two weeks injection (26.24%). Parents who had used multiple AD treatments were more likely to accept an injection over a tablet, as were older parents (P = 0.04255), parents of older children (P = 0.0109), and parents of children with higher PO-SCORAD scores (P = 0.00598) (Figure 1 and Figure 2).

Parents placed a higher value on the safety (81.45%) of the medication compared to its efficacy (18.55%). A trend was observed, especially among parents of children who took multiple treatments (P = 0.111). Older parents more frequently prioritized efficacy over safety (P = 1.75E-04). The prioritization of the drug effectiveness was positively correlated with the duration since the diagnosis (P = 3.20E-04).
Table 1. Possible responses that patients could have selected regarding their preferences for the novel, systemic treatment for atopic dermatitis (AD).

<table>
<thead>
<tr>
<th>First option</th>
<th>Second option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection every 2 weeks</td>
<td>or</td>
</tr>
<tr>
<td>Treatment more effective</td>
<td>or</td>
</tr>
<tr>
<td>Reduction of the dose on caregiver own</td>
<td>or</td>
</tr>
<tr>
<td>Withdrawal of the drug on caregiver own</td>
<td>or</td>
</tr>
<tr>
<td>Drug taken more frequently &amp; effects lasting for shorter</td>
<td>or</td>
</tr>
<tr>
<td>Treatment on demand</td>
<td>or</td>
</tr>
<tr>
<td>Administration at home</td>
<td>or</td>
</tr>
<tr>
<td>First effect-alleviation of pruritus</td>
<td>or</td>
</tr>
<tr>
<td>Lasting effect-alleviation of pruritus</td>
<td>or</td>
</tr>
</tbody>
</table>

Table 1.

<table>
<thead>
<tr>
<th>Possible responses that patients could have selected regarding their preferences for the novel, systemic treatment for atopic dermatitis (AD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>First option</td>
</tr>
<tr>
<td>Injection every 2 weeks</td>
</tr>
<tr>
<td>Treatment more effective</td>
</tr>
<tr>
<td>Reduction of the dose on caregiver own</td>
</tr>
<tr>
<td>Withdrawal of the drug on caregiver own</td>
</tr>
<tr>
<td>Drug taken more frequently &amp; effects lasting for shorter</td>
</tr>
<tr>
<td>Treatment on demand</td>
</tr>
<tr>
<td>Administration at home</td>
</tr>
<tr>
<td>First effect-alleviation of pruritus</td>
</tr>
<tr>
<td>Lasting effect-alleviation of pruritus</td>
</tr>
</tbody>
</table>

Figure 1. The presented graph depicts the variations in the likelihood of choosing generally preferred attributes (once-daily tablet, safety, less frequent administration, on-demand treatment, and administration at home) across parents of children from different age groups. Children were categorized into three distinct subgroups based on their age: those who were under the age of 5, those who were between the ages of 6 and 10, and those who were over the age of 11.

Figure 2. The presented graph depicts the variations in the likelihood of choosing generally preferred attributes (once-daily tablet, safety, less frequent administration, on-demand treatment, and administration at home) across parents of children with different disease severity. Children were divided into three subgroups depending on severity of atopic dermatitis (AD) assessed by Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) (PO-SCORAD: less than 25- mild AD, between 25 and 50- moderate AD, more than 50-severe AD).
Individuals who had older children (P = 0.03822) and those who have attempted more treatment options in the past (P = 0.01755) were more likely to choose administration in a medical facility, even though administration at home was more popular overall.

The most important early effect of the medication was the alleviation of pruritus (73.3%), while the most desired long-term result was a decrease in the severity of the skin lesions (67.87%).

Conclusions

Previous research has indicated that adult patients generally prioritize efficacy, whereas parents tend to prioritize safety. It is in line with our study. Given the parents heightened concern for their children safety, it may be significant to engage in a dialogue, as failure to do so could result in poor compliance and adherence [3].

Parents are also unwilling to accept a medication in an injection form, as supported by our study [9]. It is a well-established fact that the experience of pain can be intensified by fear, therefore, prior to the implementation of an injection therapy, it may be beneficial to provide parents with the option of enrolling their children in a needle-based educational experience [4]. Many parents of children may experience “decisional conflict”, which is characterized by confusion regarding the optimal treatment option among competing alternatives [5]. The study revealed that parents of children with AD have a tendency to favor particular characteristics of novel medications. Doctors should take parental concerns into account, especially when considering a new medication that may raise many parental concerns.

References

4. Kajikawa N, Maeno T, Maeno T. Does a child’s fear of needles decrease through a learning event with needles? Issues Compr
An Unusual Cause of Scalp Nodule in a Toddler

Smriti Gupta1, Dipankar De1, Sanjeev Handa1, Debajyoti Chatterjee2, Rahul Mahajan1

1 Department of Dermatology, Venereology and Leprology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
2 Department of Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Key words: Angiolymphoid hyperplasia with eosinophilia, propranolol, juvenile xanthogranuloma, solitary mastocytoma

Citation: Gupta S, De Dipankar, Handa S, Chatterjee D, Mahajan R. An Unusual Cause of Scalp Nodule in a Toddler. Dermatol Pract Concept. 2024;14(2):e2024110. DOI: https://doi.org/10.5826/dpc.1402a110

Accepted: November 15, 2023; Published: April 2024

Copyright: ©2024 Gupta et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Rahul Mahajan, Associate Professor, Department of Dermatology, Venereology and Leprology, Post Graduate Institute of Medical Education and Research, Chandigarh, India-160012. Email: drrahulpgi@yahoo.com

Introduction

Angiolymphoid hyperplasia with eosinophilia (ALHE), also known as epithelioid hemangioma, is an uncommon benign proliferative disorder of vessel of uncertain origin. It presents as red-to-brown papules or nodules involving the head and neck area. It involves the scalp in up to 17% of cases. It is predominantly asymptomatic but can sometimes be pruritic, painful, or bleed. The mean age at presentation is 37 years, and there is no association with patients’ sex [1]. ALHE is rarely reported in children, and the few reported sites include the lips and arms [2, 3].

Case Presentation

A three-year-old female was brought by her mother to the dermatology outpatient department with complaints of a single itchy red-colored lesion over the scalp for one year. There was no history suggestive of prior trauma and bleeding. On examination, a firm 2x2 cm erythematous nodule with no surface changes was present over the right parietal area (Figure 1a). Darier sign was negative. With the clinical differentials of solitary mastocytoma, juvenile xanthogranuloma, and ALHE, a skin biopsy was performed. Histopathological examination revealed compact orthokeratosis in epidermis. The dermis showed moderate-to-dense mixed infiltrate comprising of lymphocytes and eosinophils along with proliferating endothelial cells. A few small lymphocytes aggregates were seen (Figure 2a-b). The final diagnosis of ALHE was made, and various treatment options were discussed with the parents. Owing to the age of the child, her parents did not opt for any surgical intervention, and after appropriate counselling, she was started on oral propranolol, which was slowly titrated to the dose of 2 mg/kg over two weeks. At eight-week follow-up, marked resolution of the lesion was observed (Figure 1b).

Conclusions

Scalp nodules can have various causes, and their diagnosis is primarily confirmed through histopathological examination. Solitary mastocytoma was one of the close differentials as the lesion was itchy and because it frequently occurs during childhood and often appears on face, scalp, and extremities [4].
The other differential was juvenile xanthogranuloma, non-Langerhans cell histiocytosis, which affects children with a mean age of 3.3 years. It is a benign, self-limiting disorder characterized by asymptomatic nodules that are yellowish to brownish in color and typically found on the head and neck or trunk. Table 1 summarizes the differential diagnosis considered for the index case, along with clinical features, histopathological findings, and treatment options.

ALHE responds best to surgical excision, with the lowest recurrence rates. Other treatment options include CO2 laser, pulsed dye laser, cryotherapy, and intralesional corticosteroids, all of which have varying rates of success. Several oral medical therapies, such as dapsone, isotretinoin, and pentoxifylline, have been attempted, with very high rates of treatment failure [1]. Furthermore, there have been reports of propranolol showing positive responses in adults with ALHE, and we applied this treatment approach with similar favorable outcomes [5]. The probable mechanism by which propranolol acts in ALHE is by targeting the proliferative vascular endothelium [5]. In conclusion, ALHE should be considered as an important differential diagnosis in cases of scalp nodules in children, and propranolol can serve as an effective alternative medical therapy when surgical excision is deferred.
Table 1. Differential diagnosis of scalp nodule in index case.

<table>
<thead>
<tr>
<th></th>
<th>Angiolympoid hyperplasia with eosinophilia</th>
<th>Solitary mastocytoma</th>
<th>Juvenile xanthogranuloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td>Presents as solitary or multiple reddish-to-brown papules and nodules most commonly in head and neck area. Mostly asymptomatic but can be pruritic, painful, or can bleed [1].</td>
<td>Presents as asymptomatic solitary or multiple yellowish-to-brown papules and nodules. Commonly located on head and neck area, sometimes on trunk.</td>
<td>Solitary or multiple erythematous to yellowish nodules commonly involving head and neck area [6].</td>
</tr>
<tr>
<td>Histopathological findings</td>
<td>There is proliferation of blood vessels in the dermis which are lined by plumped endothelial cells containing eosinophilic cytoplasm and vesicular nucleus. Surrounding these proliferating vessels are lymphocytes and eosinophils which may infiltrate these vessels [2].</td>
<td>Epidermis shows increased melanization in the basal layer and dermis reveals infiltrates of mast cells mostly in upper part. These mast cells are best observed using special stains like toluidine blue and Giemsa stain [4].</td>
<td>The lesion consists of histiocytoid mononuclear cells, with oval-shaped clefted nuclei and intracytoplasmic lipid. The lipid component varies in the cytoplasm. Touton-type giant cells can be numerous. Variable numbers of lymphocytes and eosinophils can be present in the surrounding areas along with hyalinized collagen [6].</td>
</tr>
</tbody>
</table>

References

Could Conventional, Ultraviolet-Induced Fluorescence and Sub-Ultraviolet Reflectance Dermatoscopy Assist the Diagnosis of Cutaneous Collagenous Vasculopathy? A Case Report

Paweł Pietkiewicz1,2, Adarsha Adhikari3, Katarzyna Kowalska4, Agnieszka Malińska4, Monika Bowszyc-Dmochowska5

1 Dermatology Private Practice, Poznań, Poland
2 Polish Dermatoscopy Group, Poznań, Poland
3 Gandaki Medical College, Pokhara, Nepal
4 Histology and Embryology Department, Poznan University of Medical Sciences, Poznan, Poland
5 Cutaneous Histopathology and Immunopathology Section, Department of Dermatology, Poznań University of Medical Sciences, Poznań, Poland

Key words: ultraviolet radiation, dermoscopy, telangiectasia, endothelial damage, imaging

Introduction

Cutaneous collagenous vasculopathy (CCV) is an uncommon yet likely underreported idiopathic microangiopathy, first described in 2000 [1]. The disorder is characterized by progressive, asymptomatic cutaneous telangiectasias associated with collagen IV deposition around the affected vessels in the superficial dermis [1]. CCV may mimic other telangiectatic disorders, particularly generalized essential telangiectasia (GET) or pigmented purpuric dermatoses.

Case Presentation

A 50-year-old male presented with progressive patchy erythematous/telangiectatic non-atrophic macules symmetrically distributed over extensor aspects of arms and forearms that had developed over the previous three years (Figure 1A, B). He had no history of sunburns, occupational sun exposure, radiation, topical glucocorticosteroid application, hypertension, alcohol abuse, or of taking any medications. However, he has been a car parts reseller and thus,
Figure 1. Clinical presentation of erythematotelangiectatic macules distributed over extensor surfaces of the arms and forearms in 50-year-old male (A, B).

Contact polarized dermatoscopic image (DL5, Dermlite, US) of the lesion displays a vascular pattern of thick linear serpentine vessels with alternating regions of constrictions and dilations (a sausage-string appearance) of reticular/polygonal arrangement (better seen in the box) (C). Ultraviolet-induced fluorescence dermatoscopy (365nm) (DL5, Dermlite, US) demonstrates vascular constrictions and dilations (a sausage-string appearance) of reticular/polygonal arrangement along with darkening of perivascular structureless areas (higher absorption of UV spectrum by hemoglobin) suggestive of underlying endothelial dysfunction and erythrocyte extravasation (better seen in the box) (D).

Sub-ultraviolet reflectance dermatoscopy (405nm) (DZ-D100, Casio, Japan) exhibits hyporeflective linear serpentine reticular/polygonal vessels with indistinct contours (higher absorption of UV spectrum by hemoglobin) suggestive of underlying endothelial dysfunction and erythrocyte extravasation (better seen in the box) (E).

Pathology displays thinned epidermis with reduced papillomatosis, numerous dilated vessels of the superficial vascular plexus (no perivascular infiltrate noted), and fragmented elastin fibers in the upper dermis that could support the diagnosis of both generalized essential telangiectasia and cutaneous collagenous vasculopathy (F), but thickened hyalinized walls of the vessels support the diagnosis of the CCV (G).
Figure 2. Electron microscopy reveals focally disrupted hemidesmosomal internal/external plates in the basal layer (yellow arrowheads) with focal multiplication of basal lamina (green arrowhead) (A, B), mild dilation of superficial dermal vessels exhibiting multi-laminated and focally deformed basal laminae (suggestive for cutaneous collagenous vasculopathy) (red arrowheads) (C), and increased activity of endothelial cells. Perivascular lymphocytes and single extravasated erythrocytes can be noted (white arrowhead) (D). Focal abnormally banded (long-spaced) collagen (Luse-like bodies) in the vicinity of sensory receptors is suggestive for the diagnosis of CCV (blue arrowhead) (E).

Reportedly frequently used lacquer thinner (toluene-acetone solution) and vehicle paint.

Based on the clinical presentation, GET (bilateral nevus variant), telangiectasia macularis eruptiva perstans, and CCV were considered as possible differentials. Complete blood count, ESR, aminotransferases, fasting glucose, lipid profile, serum tryptase levels, thyroid hormones, estrogen and progesterone levels, and abdominal ultrasound were within the normal limits.

Contact polarized conventional, ultraviolet-induced fluorescence (UVFD) and sub-ultraviolet reflectance dermatoscopic (sUVRD) imaging were performed (Figure 1C). Diagnostic biopsy was evaluated with pathology (Figure 1D,E) and electron microscopy (Figure 1F, G).
Discussion

There is a certain clinical and pathological overlap between CCV and GET. Thus, the diagnosis can only be made with electron microscopy (CCV featuring multiplication and deformation of vascular basal lamina and the presence of Luse-like bodies) [1, 3], as was in our case. Here we describe a dermatoscopic pattern of alternated vascular constrictions and dilations (sausage-like appearance) which has not yet been observed in CCV [1, 4] and which may hint at endothelial instability [2]. Although non-contact polarized dermatoscopy is a gold standard in inflammoscopy, contact mode with 70% alcohol solution produced a crisper image of the vessels in all dermatoscopy subtypes due to the reduction of stratum corneum reflection. Although there were no dermatoscopic or histopathologic clues to erythrocyte extravasation, UVFD and sUVRD could support it with perivascular hyporeflective areas, which was confirmed with electron microscopy. We hypothesize that disruption of vascular integrity in the reported patient could possibly result from prolonged exposure to aromatic volatile organic chemical compounds present in paint thinners, especially toluene. This substance, constituting 80% of paint thinner, has been reported to upregulate TNFα levels [5] responsible for the production of reactive oxygen species. Abrupt cutoff of telangiectatic macules sparing the hands was likely associated with the use of protective gloves.

Conclusions

CCV is a clinically challenging entity associated with endothelial damage. Even though the diagnosis can be reached with electron microscopic studies, it is possible that it may present characteristic dermatoscopic, UVFD, and sUVRD clues that may aid the diagnosis and make it technically easier and affordable.

References

Innovations in Dermoscopy Training: A Comparative Analysis of Dermoscopy Training Educational Delivery Models for Resident Physicians

T. Austin Black¹, Emelie E. Nelson¹, Anthony J. Teixeria², Travis Anthony³, Julie Simon⁴, Kelly C. Nelson⁵

¹ McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA
² Davidson College, Davidson, NC, USA
³ Department of Cancer Prevention & Control Platform, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
⁴ Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
⁵ Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Key words: dermoscopy, dermoscopy education, educational theory, educational methods, early detection


Accepted: December 13, 2023; Published: April 2024

Copyright: ©2024 Black et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: Julie Simon and Dr. Kelly C. Nelson were supported by philanthropic contributions of the Lyda Hill Foundation to the MD Anderson Melanoma MoonShots Program.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. T. Austin Black and Emelie E. Nelson have contributed equally to this work and share first authorship.

Corresponding Author: Kelly C. Nelson, MD FAAD, MD Anderson Cancer Center, 1400 Pressler St, Unit 1452, Houston, TX 77030. Email: kcnelson1@mdanderson.org

Introduction

DERMatology: Early Melanoma Detection (DERM:EMD) is a scalable, metric-driven educational intervention designed to improve dermatology resident physicians’ confidence and accuracy in evaluating skin growths via dermoscopic examination. The program launched in 2017 and runs on an academic year calendar. While the program employed live synchronous delivery via Zoom from 2017-2020, the program transitioned to asynchronous web-based delivery with the 2020/21 academic year [1]. The web-based delivery utilized Canvas as the main educational platform with two additional educational software programs: Knowbly (enabled interactive data fields where residents click on specific dermoscopic features and receive feedback) and Panopto (enabled search for spoken or written word content and supported progress bars to assist with intuitive navigation through the lectures) [2-4]. We hypothesized the web-based delivery would be non-inferior to live delivery in supporting knowledge and confidence gains among dermatology residents.

Case Presentation

DERM:EMD employs two assessments: the Cutaneous Neoplasm Diagnostic Self-Efficacy Instrument (CNDSEI)
to measure confidence in diagnosing skin tumors via clinical or dermoscopic examination, and the Long Dermoscopy Assessment (LDA) to measure diagnostic accuracy [5]. Assessments are collected before and immediately after the educational exposure and at the end of the academic year to assess knowledge retention. While collection of the pre-exposure and year-end data has been consistent, completion rates for the immediate post-exposure data have varied significantly. As participants are encouraged to take the course multiple times throughout residency, only data derived from the first instance in which a resident completed both the pre- and year-end assessments within the same academic year were analyzed.

Scores collected at the course start and year-end were consolidated, and the percent mean improvement between live (2018/19, 2019/20) and web-based (2020/21, 2021/22) delivery years were compared. No difference was found in confidence gains when comparing the live and web-based delivery years (CNDSEI 10.04 vs 11.38, $P=0.348$, 95% CI: -21.54–7.61, Figure 1a). However, residents completing the web-based delivery demonstrated greater gains in diagnostic accuracy compared to the live-delivery residents (LDA 10.49 vs 7.8, $P=0.049$, 95% CI: -1.54– -0.002, Figure 1b).

Transitioning to a web-based asynchronous delivery model correlated with an expanded reach of DERM:EMD. In 2018/19, 10 dermatology residency programs participated in DERM:EMD; in 2022/23, 31 programs participated. This increase directly translates to the potential number of patients impacted by the course. At year-end, residents estimated the average weekly number of skin cancer patients they had cared for over the preceding month. This estimate was then multiplied by 47 to account for elective and vacation weeks, providing a conservative yearly approximation of patient reach (Figure 2). With the implementation of the web-based delivery method, the estimated patient reach more than doubled compared to live-delivery (237,797 vs. 706,575).

**Conclusion**

The web-based delivery supported greater outcomes over the live-delivery in two ways: first, the ability to revisit course material over time and accommodate diverse learning styles supported greater knowledge gains; second, the improved scheduling flexibility supported expanded programmatic, and therefore patient, reach. Similar delivery methods could be considered for other specialty dermatology residency education topics.
References

2. Canvas LMS. Version 2023-09-16.9. Salt Lake City, UT: Instructure, Inc; 2023
Prominent Skin Markings on the Dermoscopic Evaluation of Melanocytic Lesions: The Importance of Context

Laura Mateu-Arrom¹, Cristina López-Sánchez¹, Oriol Yélamos¹,²

¹ Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Institut d’Investigació Biomèdica Sant Pau (IIB SANT PAU), Universitat Autònoma de Barcelona, Barcelona, Spain
² Department of Dermatology, Centro Médico Teknon-Quirónsalud, Barcelona, Spain

Key words: melanoma, prominent skin markings, dermoscopy

Introduction

Prominent skin markings (PSM) have been proposed as a new dermoscopic sign for melanoma [1]. However, this sign is controversial [2] since PSM are also found in photodamaged skin [3]. Our aim was to present two cases of patients presenting melanocytic lesions with PSM, with either benign or malignant results, and highlight the importance of the context when evaluating pigmented lesions.

Case Presentation

The first case is a Caucasian 45-year-old female with a family history of melanoma (sister) who attended our dermatology clinic for full body examination. On physical examination, she had Fitzpatrick phototype III and presented with >100 pigmented lesions, many of which located on her legs. The dermoscopy of these lesions showed brown macules with a pigmented network with prominent skin markings (Figure 1A, 1B). Comparing the digital dermoscopy images present in the system, we did not identify any significant changes in these lesions for the last years, and routine yearly follow-up was proposed due to the family history of melanoma.

The second case is a Caucasian 51-year-old female, also with a family history of melanoma (mother), who was in follow-up due to multiple (>100) melanocytic nevi. The predominant dermoscopic pattern was brownish regular pigmented network, and no PSM were observed. After 10 years of follow-up, a slight growth was detected in one of the nevi located on the right ankle as well as the development of PSM (Figure 2). Excisional biopsy was performed with the result of melanoma in situ.
Discussion

PSM has been described as a dermoscopic indicator of melanoma, as seen in patient 2. However, this feature cannot be interpreted alone, since we also know that PSM can occur in lentigines [2], and we have also shown they can occur in melanocytic nevi on the legs (case 1). It has been hypothesized that PSM occur due to an alteration in rete ridges with areas showing fewer melanocytes [4]. Hence, morphology, particularly in the case of PSM, needs to be assessed in the adequate context. Besides analytical evaluation, it is crucial to compare each lesion clinically and dermoscopically (com parative recognition) to assess whether a lesion is new or not (history) and whether it is an outlier (differential recognition) [5], and also to ask the patient’s opinion, since gestalt and gut feeling of the patient and the physician have been described to have a very high positive predictive value for malignancy [6].

Conclusion

With the cases we have presented, we want to highlight the complexity in diagnosing melanoma, since pure morphology alone is sometimes not enough to render a correct diagnosis, and all available information is crucial to decide whether a lesion needs to be excised or not.

References

Granulomatous Dermatitis Characterized by the Manifestation of Tumor and Plaque Lesions Subsequent to Herpes Zoster: A Case Series

Dilek Bayramgürler¹, Abdullah Demirbaş¹, Murat Durdu², Gökţuğ Eren Aslankoç¹, Tuğrul Eruyar³, Cüyan Demirkesen³

1 Department of Dermatology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
2 Department of Dermatology, Faculty of Medicine, Başkent University, Adana, Turkey
3 Department of Pathology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

Key words: Postherpetic isotopic response, Tumor, Granulomatous reaction

Citation: Bayramgürler D, Demirbaş A, Durdu A, Aslankoç GE, Eruyar T, Demirkesen C. Granulomatous Dermatitis Characterized by the Manifestation of Tumor and Plaque Lesions Subsequent to Herpes Zoster: A Case Series. Dermatol Pract Concept. 2024;14(2):e2024129. DOI: https://doi.org/10.5826/dpc.1402a129

Accepted: December 14, 2023; Published: April 2024

Copyright: ©2024 Bayramgürler et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Introduction

Herpes zoster (HZ) is a painful vesicular dermatomal exanthem caused by the reactivation of the latent varicella zoster virus in cutaneous sensory nerves. It is more common in immunocompromised patients and can lead to complications like postherpetic neuralgia and secondary bacterial infections [1]. Postherpetic isotopic response (PHIR) is a rare chronic cutaneous reaction that can cause new skin diseases independent of previous ones [2]. Herein, we report two cases of PHIR-granulomatous disease (GD) in patients with different hematological diseases.

Case Presentations

Case 1: An 87-year-old male patient with a history of chronic lymphocytic leukemia, benign prostatic hyperplasia, and hypertension presented with painless bruising and swelling on the inner side of his left thigh for nine months. The patient stated that he had an HZ infection 1.5 years ago, and the affected area matched the current lesion area. The lesion was a 10 x 10 cm tumor with a brown livid color and a pendulous appearance. A dermatological examination revealed a brown-purple flaccid tumor on the medial aspect of the left thigh along with keratotic plugs on a yellowish background.
The differential diagnosis included B-cell lymphoma, anaplastic large cell lymphoma, granulomatous loose skin syndrome, and tuberculosis based on the clinical presentation. Histopathological examination of the lesion revealed well-formed granuloma structures, mononuclear inflammatory cell infiltration, and fragmented elastic fibers (Figure 1C). Immunohistochemical studies showed CD20+, CD2, CD3, CD5, CD7, CD8, and CD4+. The patient’s PPD
was 0 mm, and the Quantiferon test was negative, as were the tuberculosis polymerase chain reaction and deep fungal culture. PHIR-GD was diagnosed. The patient received intralesional steroid injections once a month for four months, and after significant regression of the lesions, topical steroids were continued (Figure 1D).

**Case 2:** A 68-year-old male patient with myelodysplastic syndrome presented with a painless rash on his right buttock and thigh for six months. He had had an HZ infection two years prior, which matched the current lesion area. Dermatological examination revealed erythematous papules and plaques on the right gluteal area and posterior aspect of the thigh (Figure 2A). Histopathological examination revealed a compact hyperkeratosis layer, acanthosis in the epidermis, flattening of rete projections, scattered eosinophil exocytosis, vacuolization, focal subepidermal separation in the basal layer, and granulomatous lymphohistiocytic infiltration in the dermis. While collagen degeneration and mucin deposition, which support interstitial granulomatous drug-related dermatitis, were not observed in this case, multinucleated giant cells that phagocytosed elastotic fibers were detected (Figure 2A and B). The patient was diagnosed with PHIR-GD and started on clobetasol propionate ointment, which resolved within two months with atrophic scars (Figure 2D).

**Conclusions**

Wolf’s isotopic response is a phenomenon where a healed skin condition reappears at the same site, causing a new condition. The cause is unknown, but it is suggested to be an immunosuppressed region [1-3]. This area becomes susceptible to infections, tumors, and immune disorders.

Chronic lymphedema, herpetic infections, vaccinations, and physical injuries can damage the cutaneous site, making it vulnerable. The most common isotopic response is PHIR, which is characterized by papules or plaques, patchy or nodular lesions, and hyperpigmentation [1-4]. Most cases have immunosuppressive and hematological malignancies, and both cases have hematological malignancies [1-5]. Topical steroids are commonly used in treating PHIR-GD cases [1-5], but no case has been treated with intralesional steroids. In conclusion, PHIR-GD can cause tumoral lesions, and intralesional corticosteroid therapy can be used for tumor management.

**References**

Hereditary Angioedema Exacerbated by Estrogen Supplementation Treatment for Uterine Fibroid: A Therapeutic Challenge

Alicja Mesjasz¹, Kinga Bojahr¹, Jan Romantowski¹, Marek Niedoszytko¹

¹ Department of Allergology, Faculty of Medicine, Medical University of Gdansk, Poland

Key words: hereditary angioedema, HAE, HAE type II


Accepted: December 14, 2023; Published: April 2024

Copyright: ©2024 Mesjasz et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. Alicja Mesjasz and Kinga Bojahr contributed equally to this work.

Corresponding Author: Kinga Bojahr, Department of Allergology, Faculty of Medicine, Medical University of Gdansk, Poland. Telephone: +48-798-732-181 Email: kingabojahr@gumed.edu.pl

Introduction

Hereditary angioedema (HAE) type 2 is a rare genetic disease caused by the decreased activity of C1-inhibitor (C1-INH), resulting in an increased bradykinin level in the blood [1]. There are several known triggers for exacerbations, including physical trauma, stress, or drugs, including angiotensin converting enzyme (ACE) inhibitors [1]. The clinical manifestations of HAE comprise recurrent episodes of subcutaneous and submucosal edema in any part of the body, although the face, neck, limbs, gastrointestinal tract, and genitalia are most commonly affected [2].

Case Presentation

A 30-year-old female in good general condition was admitted to the hospital with swollen joints and erythema marginatum on her wrists, palms, and around mammary papillae. The patient had neither a family history of similar symptoms nor had she previously experienced them. Initially, rheumatoid arthritis was suggested, though the diagnosis was not confirmed (European Alliance of Associations for Rheumatology guidelines; EULAR), and with symptoms receding, the patient was discharged from the hospital. Just before hospitalization, she had started taking ethinylestradiol and levonorgestrel combination contraceptive pills to reduce bleeding associated with uterine fibroid.

In the following months, the patient experienced recurrent abdominal pain and limb angioedema episodes. However, five months later, symptoms became more severe, and face angioedema was also accompanied by problems with swallowing (Figures 1 and 2). The patient had taken a high dose of antihistamines and systemic steroids at home, followed by epinephrine administration later in
the Emergency Department. She did not respond to the therapy but demonstrated gradual improvement over the course of time. With normal C1-INH serum concentration (0.17 G/L) and its low activity (28%), the final diagnosis was HAE type 2 [2]. The patient was instructed to avoid taking any medications containing estrogen and was given a plasma-derived C1-INH as a severe attack treatment and short-term prophylaxis. Nonetheless, due to the vaginal infection, the patient has used vaginal globules with estriol and Lactobacillus acidophilus, which triggered the symptoms of HAE type 2 again.

Overall, the withdrawal of estrogen hormone supplementation improved the symptoms significantly. However, management of uterine fibroid treatment was also required. As the uterine fibroid was difficult to operate, and a hysterectomy was not a reasonable option for such a young patient, progesterone-only contraceptive pills were administered, with positive outcomes.

Conclusions

The attacks of HAE type 2 may be fatal, especially because the treatment used in allergic histamine-dependent angioedema is not effective in bradykinin-dependent HAE type 2 [3]. Therefore, it is necessary to raise awareness of this rare disease.

References

Introduction

Recently, Barreto et al. described a new clinical observation in frontal fibrosing alopecia (FFA) – the “watch sign” [1]. The authors described two males in whom, despite involvement of forearms, hair loss spared the area regularly covered by a wristwatch.

Herein we present two additional male FFA patients attending our dermatology outpatient clinic screened for this novel sign.

Case presentation

The first patient was a 79-year-old male (phototype I) admitted for surgical treatment of basal cell carcinoma. Apart from the tumor, advanced recession of the hairline to the border of the parietal and occipital area of the scalp was observed (Figures 1a, 1d). In addition, clinical features of madarosis as well as loss of hair on the upper extremities were noted (Figures 1b, 1c, 1e). The patient had neither been diagnosed nor treated for FFA before. Dermoscopic evaluation of the left arm, just under the area usually occupied by his analogue watch, revealed preserved hairs, corresponding with the “watch sign” (Figures 1c, 1f).

The second patient was a 30-year-old male (phototype II) treated for FFA in a dermatology outpatient clinic for two years. On clinical examination, minor recession of frontotemporal hairline with erythema and accompanying madarosis were observed (Figures 2a, 2b, 2d, 2e). The patient had previously been treated with topical corticosteroids, isotretinoin, triamcinolone acetonide mesotherapy, and oral minoxidil. Additionally, bimatoprost and tacrolimus were applied on the eyebrow area. The patient reported wearing a smartwatch on his left wrist on a daily basis. However, forearms were not affected by the disease, and dermoscopy did not reveal differences in hair density and structure in corresponding wrist areas on both sides (Figures 2c, 2f).
Figure 1. Clinical and trichoscopic images of the first described patient diagnosed with FFA. (a, b) Severe hair loss, with significant recession of frontotemporal hairline and partial loss of eyebrows; (c) Three terminal hairs arising on the left forearm; (d, e) Corresponding trichoscopy of scalp and eyebrows, respectively; (f) Trichoscopy of the “watch sign” on the left forearm revealed preserved hairs with mild perifollicular scaling.

FotoFinder, Medicam 800 HD, 70x magnification, immersion gel

Figure 2. Clinical and trichoscopic images of a second FFA patient. (a) Cicatricial band of frontal hairline recession with extensive perifollicular erythema. The “lonely hair” sign is also clinically visible; (b) Almost complete loss of the eyebrows; (c) Symmetrical hair distribution on both forearms, with no discernible “watch sign” (L, R – left and right forearm, respectively); (d) Trichoscopy of frontal hairline shows loss of vellus hairs and follicular openings, ivory background, perifollicular erythema, scaling, and pili torti; (e) Mild perifollicular scale is visible on eyebrow trichoscopy. Multiple yellow dots and focal erythema are also notable. (f) Trichoscopy of the left forearm does not show any clue for FFA diagnosis.

FotoFinder, Medicam 800 HD, 70x magnification, immersion gel
Conclusion

FFA is a distinct clinical subset of lichen planopilaris which causes permanent hair loss due to inflammation and subsequent scarring. Underlying factors triggering the development of FFA remain unknown. Typically, FFA initially manifests with progressive recession of the frontotemporal hairline, usually accompanied by perifollicular erythema and scaling. Furthermore, most patients experience complete or partial loss of the eyebrows, although non-glabrous skin in any location may be affected. FFA predominantly affects postmenopausal women. Fewer than 2% of FFA patients are males [2].

In contrast to the previous report, only one of the two male patients from our department presented the “watch sign”. The underlying pathomechanism of this finding remains unknown. Barreto et al. [1] in their report presented convincing exclusionary arguments concerning the possible association with sun exposure, sunscreen, moisturizer, or other cosmetic products [3, 4].

The authors suggested a mechanism related to the Renbök phenomenon. Previously, this phenomenon had been reported in the context of FFA sparing dermal melanocytic nevus and vascular nevus [5, 6]. In the case of “the watch sign,” it could be related to pathological processes in the skin induced by pressure or temperature increase associated with the use of a wristwatch.

Our observation supports the occurrence of the “watch sign” in males with FFA who wear a wristwatch. Further studies on the “watch sign” may bring new insights into disease pathogenesis.

References

Retrospective Cohort Study of Hepatic and Hematologic Toxicity in Terbinafine-Treated Onychomycosis Patients With Reduced Kidney Function at an Academic Institution

Kaya L. Curtis1, Jose W. Ricardo2, Yuqing Qiu3, Debra K. Lee4, Jamie Hedrick5, Henry I. Lipner6, Shari R. Lipner2

1 Weill Cornell Medical College, New York, New York, USA
2 Weill Cornell Medicine, Department of Dermatology, New York, New York, USA
3 Department of Population Health Sciences, Weill Cornell Medicine, New York, New York, USA
4 University of Texas Medical Branch, Galveston, Texas, USA
5 Philadelphia College of Osteopathic Medicine, Philadelphia, Pennsylvania, USA
6 Division of Nephrology, Maimonides Medical Center, Brooklyn, New York, USA

Key words: Terbinafine, onychomycosis, renal, hepatic, laboratory monitoring

Citation: Curtis KL, Ricardo JW, Qiu Y, et al. Retrospective Cohort Study of Hepatic and Hematologic Toxicity in Terbinafine-Treated Onychomycosis Patients With Reduced Kidney Function at an Academic Institution. Dermatol Pract Concept. 2024;14(2):e2024137. DOI: https://doi.org/10.5826/dpc.1402a137

Accepted: January 31, 2024; Published: April 2024

Copyright: ©2024 Curtis et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: Ms. Kaya Curtis, Dr. Jose Ricardo, Ms. Yuqing Qiu, Dr. Debra Lee, Dr. Jamie Hedrick, and Dr. Henry Lipner have no conflicts of interest relevant to the content of the submission. Financial disclosures: Dr. Shari Lipner has served as a consult for Ortho-Dermatologics, BelleTorus Corporation, Eli Lilly, and Moberg Pharmaceuticals.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Shari R. Lipner MD, PhD, 1305 York Avenue, NY, NY 10021. Phone: +1/646-962-3376 Fax: +1/646-962-0033 E-mail: shl9032@med.cornell.edu

Introduction

Oral terbinafine, a first-line onychomycosis therapy, is primarily excreted renally [1, 2]. Patients with renal impairment may have increased hepatic and hematologic toxicity risk. Onychomycosis was ~2x more common in hemodialysis and kidney transplant patients vs. non-renal disease controls in a prospective study (N=510, P=0.03) [3]. Therefore, we aimed to evaluate the association between kidney function and laboratory test abnormality rates in terbinafine-treated onychomycosis patients.

Case Presentation

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and complete blood count (CBC) tests of terbinafine-treated adults with onychomycosis (2000-2021) ≤3 months before, during, and ≤3 months after treatment were collected (Supplemental Methods).

Of 2,195 records, 734 patients were included, with an average age of 55.2 years (Supplemental Table 1). Two hundred eighty-five patients had abnormal renal function, and proportion of abnormal AST, ALT, and CBC values
were similar during and post-terbinafine treatment vs. pre-treatment (Supplemental Table 2). After matching for age, sex, weight, hepatic/hematologic disease, terbinafine-treated stage 2 chronic renal insufficiency (CRI) vs. stage 1 CRI and stage 3 CRI vs. stage 1 CRI patients had similar laboratory abnormality risk during and post-treatment vs. baseline (Table 1). Stage 1 CRI patients had mean 0.02mg/dL serum creatinine change from baseline to during treatment and baseline to post-treatment (both 95% CI: 0.01–0.04, \( P=0.002 \), \( P=0.005 \), respectively). Mean creatinine was stable from baseline to during and post-treatment for stages 2 and 3 CRI (Supplemental Table 3).

**Discussion**

Our study suggests that terbinafine-treated onychomycosis patients with stages 2 or 3 CRI are not at increased risk of developing laboratory abnormalities vs. patients with normal kidney function (stage 1 CRI). Creatinine increased in stage 1 CRI terbinafine-treated patients, which may be due to laboratory variations and was clinically insignificant.

We found no difference between baseline and monitoring hepatic and hematologic laboratory values, similar to a retrospective cohort study [4] of 4,309 terbinafine courses for dermatophyte infection (majority onychomycosis), where transaminitis, anemia, lymphopenia, and neutropenia rates were low and comparable to baseline. In a population-based study [5] of 12,376 patients, incidence of terbinafine-induced liver injury was 1.6/10,000 persons.

Since terbinafine is primarily excreted in the urine (80%), with creatinine clearance decreased by 50% in patients with <50 mL/min [1], reducing daily terbinafine dosage by half has been suggested for patients with reduced renal function [2]. However, the package insert does not mention dose reduction

| Table 1. Risk of developing laboratory abnormalities in terbinafine-treated patients with Stage 2/Stage 3 CRI compared to patients with stage 1 CRI* |
|---------------------------------|-----------------|-----------------|---|
| **Stage 2 CRI compared to stage 1 CRI** | **Outcome variable** | **Odds ratio** | **95% confidence interval** | **P value** |
| Abnormal AST results post-treatment | 1.21 | 0–715.34 | 0.131 |
| Abnormal AST results during treatment | 0.85 | 0.36–2.02 | 0.717 |
| Abnormal ALT results post-treatment | 0.29 | 0.06–1.48 | 0.137 |
| Abnormal ALT results during treatment | 0.98 | 0–644.37 | 0.994 |
| Abnormal CBC results post-treatment | 1.01 | 0.4–2.55 | 0.981 |
| Abnormal CBC results during treatment | 1.49 | 0.67–3.3 | 0.329 |

| **Stage 3 CRI compared to stage 1 CRI** | **Outcome variable** | **Odds ratio** | **95% confidence interval** | **P value** |
| Abnormal AST results post-treatment** | -- | -- | -- |
| Abnormal AST results during treatment | 0.9 | 0.11–7.17 | 0.924 |
| Abnormal ALT results post-treatment*** | -- | -- | -- |
| Abnormal ALT results during treatment*** | -- | -- | -- |
| Abnormal CBC results post-treatment | 3.66 | 0.5–26.79 | 0.202 |
| Abnormal CBC results during treatment | 3.35 | 0.54–20.82 | 0.194 |

*After matching and adjusting for covariates, including age, sex, weight, presence of hepatic/hematologic disease, and baseline AST, ALT, CBC laboratory tests.

**Odds ratios could not be calculated due to lack of laboratory values in stage 1 or stage 3 groups.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; CRI: chronic renal insufficiency.
in renally impaired patients [1], with a paucity of studies to support this recommendation. In a retrospective study of 13 kidney transplant recipients (creatinine <3.39 mg/dL) treated with terbinafine (250 mg daily, 12 weeks) for onychomycosis, none had hepatic or hematologic abnormalities, suggesting that terbinafine may be safe even in patients with severely reduced kidney function [4].

Limitations include small sample size, confounding bias, single-center design, and lack of consideration of dosage and adverse event-related treatment interruptions. Few patients had severe renal impairment.

Conclusions

In sum, onychomycosis patients with mild to moderate reduced kidney function do not seem to have increased risk of developing laboratory abnormalities with terbinafine treatment, and dose reduction may not be necessary. We recommend checking baseline creatinine to evaluate renal function before prescribing terbinafine for onychomycosis treatment, pending larger multicenter trials evaluating onychomycosis patients with kidney disease.

References

Circumscribed Acranal Hypokeratosis: Clinical and Dermoscopic Signs of an Evolving Condition

Alessandra Petruzzellis¹, Eleonora Di Matteo¹, Luca Bianchi¹, Francesca Lupi², Ornella De Pita², Giuseppe Cianchini²

¹Dermatology Unit, Fondazione Policlinico Tor Vergata, Tor Vergata University of Rome, Rome, Italy
²UOC Clinical Pathology and Autoimmune and Inflammatory Diseases of the Skin. Cristo Re Hospital, Rome, Italy

Key words: hypokeratosis, dermoscopy, rare disease


Accepted: January 10, 2024; Published: April 2024

Copyright: ©2024 Petruzzellis et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
Corresponding Author: Alessandra Petruzzellis, Dermatology Unit, Fondazione Policlinico Tor Vergata, Tor Vergata University of Rome, Viale Oxford 81, 00133 Rome, Italy. Email: alessandrapetruzzellis.ap@gmail.com

Introduction

Circumscribed acral hypokeratosis (CAH) is a rare skin condition with an unknown cause, with fewer than 100 reported cases to date. Typically found on the thenar and hypothenar eminences of middle-aged females, it manifests as asymptomatic depressed erythematous patches with well-demarcated borders [1]. There may be one of more lesions, which persist for extended periods. While malignant transformation is rare, it has been documented in a few cases. Histologically, the epidermal depression corresponds to a reduction in the cornified layer, and the elevated borders indicate hyperkeratosis between the lesion and normal skin [2].

Dermoscopically, the central depressed area exhibits an erythematous pattern with dotted vessels and vascular loops, likely due to thinning of the horny layer and dilatation of dermal capillaries. White dots correspond to the acrosyringium. The peripheral border displays a “stair step” or “geological strata” configuration with skin layer thickening [3]. These distinctive dermatoscopic features facilitate the differentiation between circumscribed palmoplantar hypokeratosis and common differentials such as Bowen disease and porokeratosis of Mibelli [4].

Case Presentation

We present 2 cases of CAH and our considerations about the correlation between clinical-dermatoscopic features and the disease activity.

A 78-year-old female presented with 2 depressed erythematosus patches on the thenar eminence, with evident elevated scaling borders and atrophy in the middle. Dermoscopy showed erythema and a vascular pattern characterized by dotted vessels and white loops in the center and geological strata aspects in the periphery. The patient reported that these lesions had appeared 4 months before and were increasing in size (Figure 1, A and B).

A 60-year-old female presented with 2 lesions on the hypothenar eminences of both hands, which looked like 2 slightly erythematous atrophic patches with scaly borders.
Dermoscopy showed a uniform erythematous pattern with some telangiectasias and a border without the typical geological strata look. These lesions were reported to have been stable for 2 years (Figure 1, C and D).

Conclusions

We hypothesize that the different onset date and evolution might be connected to the slightly different aspects of the lesions. The first patient shows 2 evolving lesions with recent onset, presenting a clear elevated border with the geological strata feature and a rich vascular pattern, while the second had a more stable condition and less evident vessels and peripheral borders. Our hypothesis is that these characteristics, in particular the one on the border, are connected to disease activity, showing a more erythematous vascular pattern with well elevated borders when the lesions are evolving and increasing, and with a low slightly scaly border without a rich vascular aspect in the quiescent phase. This theory fits perfectly with the timing of disease activity in our patients.

Our longstanding lesion findings differ from those recently described by Majluf-Cáceres et al., who reported elongated white structures and a fine white pseudonetwork and hypothesized a correlation with increasing collagen proliferation and thickening [5].

Further research should be conducted with more clinical cases in order to confirm our hypothesis and to deepen our knowledge of the pathogenesis and the evolution.

References

2. F. Urbina, A. Pérez, L. Requena, A. Rütten, Circumscribed Palmar or Plantar Hypokeratosis 10 Years After the First Description:


Dermoscopy of Thick Scalp Melanoma: Is It Always an Easy Diagnosis?

Sebastiano Pellerone¹, Chiara Pensa², Giustino Riccio¹, Gabriella Brancaccio¹, Giuseppe Argenziano¹, Elvira Moscarella¹

¹Dermatology Unit, University of Campania Vanvitelli, Naples, Italy
²Dermatology Unit, Tor Vergata University, Rome, Italy

Key words: Scalp melanoma, thick melanoma, Dermoscopy

Introduction

Scalp melanoma (SM) tends to present a greater invasiveness at diagnosis and a worst prognosis compared to cutaneous melanomas at other body sites [1]. Previous studies have investigated the dermoscopic features of SM, mainly focusing on thin melanomas [2,3]. Little is known about dermoscopic features of thick (>0.8 mm Breslow) melanoma of the scalp [4,5,6].

Case Presentation

This was a retrospective case control study conducted at the Dermatology Unit of the University of Campania Vanvitelli, Naples, Italy. We identified 30 cases of scalp melanoma with a Breslow thickness equal to or greater than 0.8 mm and compared them to a control group of 63 dorsal melanomas matched for thickness, age, and ulceration. Clinical characteristics of the patients were gathered and tabulated, dermoscopy images were analyzed by three observers in consensus (EM, SP, CP). Statistical analysis was performed using the R statistical software, version 4.0. Continuous and categorical data are presented as means and frequencies and were compared using T-student test and Pearson’s Chi-squared test or the Fisher’ Exact test, when appropriate. The Type I error probability associated with all tests in this study was set to 0.05.

Clinical and dermoscopic features are summarized in Table S1. The great majority of patients with SM were men (90%, p-value 0.01). SM presented dermoscopic features related to lentigo maligna subtype in a significantly higher percentage than melanoma on the back. (Table S1). Examining the overall pattern of lesions, we categorized scalp melanoma cases into six main groups. Lentigo maligna melanoma group (n=12, 40%) displaying dermoscopic features typical of lentigo maligna melanoma, such as pseudonetwork and obliteration of hair follicles. Blue-Black positive cases (n=12, 40%) positive to the blue black rule. Basal cell carcinoma-like

1 Dermatology Unit, University of Campania Vanvitelli, Naples, Italy
2 Dermatology Unit, Tor Vergata University, Rome, Italy

Copyright: ©2024 Pellerone et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Sebastiano Pellerone, Dermatology Clinic, Via Sergio Pansini n.5, 84081, Napoli, Italy. Telephone: 0039 3519636607, Email: pseba90@gmail.com
cases (n 2, 6.7%) showing arborizing vessels and ulceration. Angioma-like lesions (n 2, 6.7%) showing vascular lacunae.

Two cases displayed typical features for squamous cell carcinoma and seborrhic keratosis, namely white structureless areas and a whitish collar of the lesion and, light brown fingerprint-like parallel structures respectively (Figure 1 and 2).

Only few studies have focused on dermoscopic characteristics of scalp melanoma. In the study by Stanganelli et al. [3] authors concluded that thin SM tends to display network

Figure 1. (A, D) Invasive melanoma in a 75 year-old man. The flat brown macule was arising in hair bearing scalp (A). In dermoscopy atypical pseudo-network and regression are detected. (B, E) Invasive melanoma on the parietal region in a 63-year-old man with androgenic alopecia, 2 mm Breslow thickness. Clinically, the lesion appears as a black, eroded nodule and satellitosis is already visible (B). In dermoscopy the lesion is positive for the blue-black rule (E). (C; F) Invasive melanoma on the scalp of a 66-year-old woman, 39 mm Breslow thickness, pT4b. Clinically, the lesion appears nodular and exophytic (C). In dermoscopy milky red areas and large arborising vessels are found on a white background (F).

Figure 2. (A, C) Invasive melanoma on the parietal region in a 70-year-old man with androgenic alopecia, Breslow thickness 3 mm. Clinically, it mimics an extended angioma (A). In dermoscopy, white streaks are found all over the lesion (C). (B, D) Invasive melanoma on the frontal region in a 75-year-old man with androgenic alopecia, superficial spreading melanoma 3.3 mm Breslow thickness. Clinically, the lesion appears partially nodular with ill defined borders (B). In dermoscopy a unspecific pattern is detected with brownish pigmentation, white lines and milky red areas (D).
or pseudo network with regression as main features, thick scalp melanoma was categorized as unspecific in its dermoscopic appearance. In our study we confirm the variegated dermoscopic appearance of SM that can show features typical for non melanoma skin cancer. Since NMSC are very often found on the scalp, making an accurate preoperative diagnosis is crucial because the tumors may need a different management approach. As expected, the main features differentiating thick SM from melanomas located on the back were those related to the lentigo maligna subtype of melanoma. Regarding the other dermoscopic features, micro ulceration, arborizing blood vessels and pink structureless areas were more frequent in SM, even if the data were not statistically significant.

Conclusion

Thick SM often exhibit characteristics typical of head and neck melanomas. Most of our cases demonstrated features resembling lentigo maligna melanoma (40%) or were positive for the blue-black rule (40%). A smaller number of cases (20%) could be indistinguishable from non-melanocytic lesions such as basal cell carcinomas, squamous cell carcinomas, angiomas, or seborrheic keratoses, making clinical-dermoscopic diagnosis challenging.

References


Case Presentation

A 34-year-old male presented with a 7-year history of slowly increasing, multiple 3–4 mm, papular lesions on the bilateral gluteal region (Figure 1A). He had been diagnosed with genital wart and lichen simplex chronicus previously, and topical therapies, including topical corticosteroids, 5-FU, podophyllotoxin, and cryotherapy, had been offered to him; he stated that he had had no benefit from previous treatments. In dermoscopic examination, sharply demarcated hyperpigmented hyperkeratotic peripheral rim with a light brown hyperpigmentation, center with yellowish and whitish scales, and white structureless areas were detected (Figure 1B-1C). Histologically, irregular acanthosis, and cornoid lamella formation in the areas of epidermal invagination were observed in the epidermis. The cornoid lamella structures were composed of dyskeratotic cells with granular layer loss and vacuoles under the parakeratotic column. Vacuolar degeneration was observed at the dermo-epidermal junction, and perivascular lymphocyte infiltration was observed around the dilated capillary vessel (Figure 1D). The patient was treated with Er:YAG laser.

Teaching Point

Porokeratosis ptychotropica (PP) is a rare variant of porokeratosis that is characterized by symmetrical dyskeratotic skin lesions on the gluteal clefts [1]. It was first described by Lucker et al. in 1995, and to date, few cases have been reported in the literature. PP may be misdiagnosed as psoriasis, eczema, epidermal nevus, candidiasis, squamous cell carcinoma, cutaneous tuberculosis, Bowen disease, or anogenital warts, as in our patient [2]. It presents clinically as a characteristic butterfly-shaped scaly plaque with a raised rim. These lesions are usually itchy, which may lead to scratching and chronic inflammation. Therapeutic options in the treatment of PP are limited and usually not curative. There are
few case reports about various treatment options, such as topical/intralesional corticosteroids, topical/ systemic retinoids, imiquimod, cholesterol, 5-fluorouracil, simvastatin, excimer laser, photodynamic therapy, intralesional bleomycin injection, cryotherapy, CO2 laser, and dermatome, and excision has been reported in the literature, but complete clearance has not been observed with almost any treatment [3,4]. In our case, focal recurrence foci were observed after ablative fractional Erbium:YAG laser treatment, although not as much as in the first visit, and follow-up with repeated laser treatments was recommended. We present this rare disorder, which has the risk of progressing into squamous cell carcinoma in the long term if left untreated, as a reminder of the differential diagnosis of many benign and malignant anogenital dermatoses.

References


Figure 1. (A) Clinical presentation of itchy hyperkeratotic popular lesions on gluteal cleft (B-C) Hyperpigmented hyperkeratotic peripheral rim with a light brown hyperpigmentation, center with yellowish and whitish scales, and white structureless areas were seen at dermoscopy (D) A cornoid lamella in porokeratosis. A thin column of parakeratotic cells overlies a narrow zone in which the granular layer has disappeared. Vacuolar degeneration was observed at the dermoepidermal junction, and perivascular lymphocyte infiltration was observed around the dilated capillary vessel in dermis (H&E, 10×10).
Human Cutaneous Dirofilariasis Caused by *Dirofilaria repens*

Victoria Mattutzu¹, Céline Nourrisson², Clément Theis⁴, Carole Chevenet¹, Philippe Poirier²,³, Maxime Moniot²

1 Department of Pathological Anatomy and Cytology, University Hospital Center of Clermont-Ferrand, France
2 Department of Parasitology-Mycology, University Hospital Center of Clermont-Ferrand, 3HP, France
3 Microbes, Intestin, Inflammation et Susceptibilité de l’Hôte (M2iSH), UMR Inserm/Université Clermont Auvergne U1071, USC INRA 2018, France
4 Department of Infectious and Tropical Diseases, University Hospital Center of Clermont-Ferrand, France

Citation: Mattutzu V, Nourrisson C, Theis C, Chevenet C, Poirier P, Moniot M. Human Cutaneous Dirofilariasis Caused by *Dirofilaria repens*. Dermatol Pract Concept. 2024;14(2):e2024102. DOI: https://doi.org/10.5826/dpc.1402a102

Accepted: September 7, 2023; Published: April 2024

Copyright: ©2024 Mattutzu et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Dr Maxime Moniot, Service de Parasitologie Mycologie, 58 rue Montalembert, CHU Gabriel Montpied, 63003 Clermont-Ferrand Cedex 1, France. Phone number: +33 (0)4 73 75 01 95 / Fax number: +33 (0)4 73 75 01 96
Email: mmoniot@chu-clermontferrand.fr

Case Presentation

A 63-year-old female was seen with a purplish subcutaneous nodule located above the glabel and measuring 6 mm in diameter. The lesion had a rapid onset and was followed, two days later, by a wing nose edema, suggestive of granuloma. The patient had no particular medical or travel history. The biological work-up did not show abnormality. Histological exam revealed a granulomatous reaction of the hypodermis, partly suppurated, with an adult worm (Figure 1A). Section of the worm measuring bout 500 µm showed the genital tubes, the muscle layer and a thick cuticle of 12 µm, laminated, with longitudinal striation (Figure 1B). *Dirofilaria repens* was suspected and confirmed by sequencing [1].

In addition to the surgical excision, the patient received a single dose of ivermectine, with no sign of recurrence six weeks later.

Teaching Point

Dirofilariasis is a cosmopolitan mosquito-transmitted disease involving nematodes of the *Dirofilaria* genus. Both *D. repens* and *D. immitis* are endemic in the Mediterranean region. The definitive hosts of *D. repens* are canids and rarely felids, Human being accidental host. *Dirofilaria repens* usually manifests as either a wandering worm in the subcutaneous tissue or a granulomatous nodule, mostly...
located in ocular and facial regions, whereas *D. immitis* usually causes pulmonary diseases. In the subcutaneous form, the elevation of blood eosinophils is inconstant. Surgical removal of the nodule is the definitive and curative treatment of dirofilariasis.

References


Figure 1. Microscopic examination of the excised nodule at the time of diagnosis after H&E staining. (A) Superficial dermis and epidermis with sections of the worm in surface (×100 magnification); (B) Section of the worm showing the genital tubes (a), the muscle layer (b), the cuticle with characteristic external longitudinal ridges (c) (×400 magnification).
A Lesion Surrounded by the Rainbow: Merkel Cell Carcinoma

Melek Aslan Kayıran¹, Ahmet Sait Şahin¹, Bengu Cobanoglu Simsek²

¹ Department of Dermatological and Venereal Diseases, Istanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yağcı City Hospital, Istanbul, Turkey
² Department of Pathology, Istanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yağcı City Hospital, Istanbul, Turkey

Citation: Kayıran MA, Şahin AS, Simsek BC. A Lesion Surrounded by the Rainbow: Merkel Cell Carcinoma. Dermatol Pract Concept. 2024;14(2):e2024064. DOI: https://doi.org/10.5826/dpc.1402a64

Accepted: October 22, 2023; Published: April 2024

Copyright: ©2024 Kayıran et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Melek Aslan Kayıran, Eğitim Mah. Kadıköy/Istanbul 34722 E-mail: melekaslan@gmail.com

Case Presentation

A 76-year-old male presented due to a mass on his left leg, which had appeared three months earlier. A firm 1 cm purple nodule was observed on the left thigh. In addition, an erythematous macule measuring approximately 10 cm in diameter around the nodule was seen (Figure 1A). Dermoscopy of the nodule revealed scattered linear telangiectasias in the center, whitish-red areas, a rainbow pattern surrounding the lesion, and scales (Figure 1B). Histopathological examination showed a tumor with a nodular growth pattern in the dermis composed of cells with a high nucleus-to-cytoplasm ratio, round-oval nuclei, and finely dispersed chromatin. The neoplastic cells exhibited positivity for cytokeratin-20 and neuroendocrine tumor markers. Merkel cell carcinoma (MCC) was diagnosed and was completely excised, with negative regional lymph nodes. Three months later, a biopsy of a mass detected on the right lumbar region was reported as renal cell carcinoma, leading to nephrectomy. The patient is regularly monitored, and no recurrence or new lesion has been detected.

Teaching Point

Although the rainbow pattern on dermoscopy is primarily associated with Kaposi sarcoma, it has also been reported in lesions such as pyogenic granuloma, strawberry hemangioma, malignant melanoma, angiookeratoma, basal cell carcinoma, dermatofibroma, and blue nevus [1]. However, a few MCC cases have only previously described the rainbow pattern [2,3]. Merkel cell carcinoma is a rare carcinoma with a poor prognosis due to its high, rapid metastasis potential. Therefore, MCC should also be considered when encountering a rapidly growing purplish solitary mass with a rainbow pattern on dermoscopy.
References


**Figure 1.** A) Firm purplish nodule on the right thigh surrounded by an erythematous macule. B) The dermoscopic view: multiple telangiectatic vessels, some of which branched, and the rainbow pattern surrounding the purple nodule. C) The tumor localized in the dermis is composed of neuroendocrine cells (HEX100). D) Positive staining with neuroendocrine markers in Merkel cell carcinoma (SynaptophysinX200).
Cutaneous Metastases as a First Sign of Gastric Adenocarcinoma

Marta Prtajin¹, Daniela Ledić Drvar¹, Daška Štulhofer Buzina¹, Ružica Jurakić Tončić¹, Ivana Ilić², Romana Ćeović¹

¹ Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia
² Department of Pathology and Cytology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

Case Presentation

A 61-year-old female patient was referred to our department with newly developed erythematous nodules on the skin of the back of her neck (Figure 1A). Concurrently, she reported unintentional weight loss, faster intestine transit time, and painful gastric spasms. She had no severe diseases history. After a year of extensive diagnostic procedures, she was diagnosed with diffuse gastric adenocarcinoma. Histopathological examination of her skin biopsy revealed cutaneous metastasis, which was confirmed with cytokeratin (CK)-7 immunohistochemical positivity (Figure 1B). Over the following year and a half, our patient underwent surgery, followed by several chemotherapy cycles. Multiple cutaneous metastases on her trunk were treated with radiotherapy, resulting in severe post-irradiation reaction. Unfortunately, despite all treatment, she passed away.

Teaching Point

Cutaneous metastasis may be the first sign of a silent primary tumor [1]. Metastatic dissemination to the skin occurs by lymphatic or hematogenous spread, direct contiguity, pericytic mimicry, or iatrogenic implantation. Metastases may appear before primary tumor identification in approximately 10% and simultaneously in 25.1% cases, but generally later in the disease course [2]. Lung cancer is accountable for most cases in men and breast cancer in women. Cutaneous metastases mostly present as nodules [1,2]. Some gastrointestinal tumors may give metastases to the umbilicus, presenting as Sister Mary Joseph nodule [1]. Clinical morphology, location, and histopathological and immunohistochemical findings of cutaneous metastases alongside patient’s sex and age are essential for diagnosing primary neoplasm [2]. Dermatologists have an important role in early recognition and differentiation of correct diagnosis [1].
References


Figure 1. (A) Clinical presentation. (B) Positive immunohistochemical staining for CK-7.
Steatocystoma Simplex of the Vulva

Anna Mishina¹, Vergil Petrovici², Ecaterina Foca²,³, Igor Mishin³

¹ Department of Surgical Gynecology, Mother and Child Institute, Chisinau, Moldova
² Department of Pathology, Mother and Child Institute, Chisinau, Moldova
³ Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova

Case Presentation

A 43-year-old female (G-1, A-1) presented to the clinic with a 2-year history of painless swelling in the left labia majora. Perineal examination was normal except for a 2 cm mass in the left labia majora, movable with soft rubbery consistency. The skin over the labia was normal, with no vascular changes. There was no inguinal lymphadenopathy. Her family history was unremarkable. Perineal ultrasound demonstrated a unicameral well-demarcated oval-shaped cyst measuring 29.5 x 13.0 mm in size, with homogeneous, hyperechogenic internal echotexture and no Doppler flow (Fig. 1A). The mass was enucleated with an intact capsule under anesthesia (Fig. 1B, C). The cyst was filled with thick, greasy material. The pathological findings of this mass were consistent with a steatocystoma (Fig. 1D). There was no recurrence during the 7-month follow-up.

Teaching Point

Steatocystoma is a lesion that results from a hamartomatous malformation of the pilosebaceous duct, leading to an epithelium-lined cystic lesion containing sebaceous lobules. Steatocystomas can be classified into steatocystoma multiplex (SCM) and steatocystoma simplex (SCS), according to the multiplicity. SCS was first reported in 1982 by Brownstein, who described 30 cases [1]. In order of decreasing frequency, these lesions are mostly located on the scalp, face, neck, axillae, chest, upper limbs, back, or lower limbs [1]. In contrast, SCM and SCS in the vulvo-perineal region is extremely rare, with only a few cases reported in the literature [2]. SCS is a rarely benign lesion occurring extremely rare on the vulva and should be considered in the differential diagnosis of painful/painless superficial vulvar mass.
References


Figure 1. (A) Perineal ultrasound demonstrated a unicameral well-demarcated oval-shaped cyst. (B) Intraoperative view of mass in the left labia majora. (C) The cyst was excised intact. (D) Histopathology: the cystic wall is serpiginous, lined by thin squamous epithelium with an outer corrugated cuticle and minimal granular layer (H&E, x20).
Bullous Kaposi Sarcoma: An Uncommon Blistering Variant in an HIV-Negative Patient

Eleonora Gherardi¹, Luca Tinunin², Tommaso Grassi³, Vincenza Maio², Vieri Grandi¹

¹ Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy
² Section of Pathology, Department of Health Sciences, University of Florence, Florence, Italy
³ Unit of Hygiene and Preventive Medicine, P. Palagi Hospital, Florence, Italy

Citation: Gherardi E, Tinunin L, Grassi T, Maio V, Grandi V. Bullous Kaposi Sarcoma: An Uncommon Blistering Variant in an HIV-Negative Patient. Dermatol Pract Concept. 2024;14(2):e2024113. DOI: https://doi.org/10.5826/dpc.1402a113

Accepted: November 17, 2023; Published: April 2024

Copyright: ©2024 Gherardi et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Eleonora Gherardi, MD, University of Florence, Department of Health Sciences, Section of Dermatology, Ospedale P. Palagi, viale Michelangiolo 41, 50125 Florence, Italy. Tel: 055-6939624 Email: eleonora.gherardi@unifi.it

Case Presentation

We present the case of an 82-year-old Italian male with a localized eruption on the lower limbs persisting for over two years. The lesions initially received treatment with local and systemic corticosteroids but showed no improvement. On examination, brownish violaceous patches, papules, plaques, and tense blisters with serous content were observed on healthy skin, primarily affecting the ankles, dorsum, fingers, and soles of the feet (Figure 1A). The patient reported no local or systemic symptoms, nor lymphedema. Histopathological analysis showed a dermal proliferation of irregular abnormal small vessels intermingled with spindle cells and a patchy lympho-histiocytic infiltrate with scattered plasma cells (Figure 1B). Additional features included slit-like spaces with erythrocytes and siderophages. Nuclear HHV8 immunohistochemical expression was demonstrated (Figure 1C). The diagnosis of bullous Kaposi sarcoma (KS) was established based on these findings. The patient was tested for HIV and resulted negative. Since the patient had no systemic symptoms, no further instrumental exams were conducted. Considering the indolent nature of the lesions and the absence of systemic involvement, the patient was managed conservatively with elastic compression therapy. Regular follow-up visits were scheduled to monitor the progress and assess treatment response. Throughout the follow-up period, no significant changes or complications were observed.

Teaching Point

Bullous Kaposi sarcoma is a rare variant of Kaposi sarcoma characterized by the presence of bullous lesions [1]. It should be considered in the differential diagnosis of blistering lesions, particularly in elderly individuals from the Mediterranean region [2]. The distinctive clinical and histopathological features contribute to its unique presentation. Various hypothesis have been proposed to elucidate the formation of vesiculobullous lesions in KS. One suggests that the local effects of the tumoral infiltration, including the occlusion of lymphatic vessels and subsequent dermal edema, may
explain the development of such lesions. Clinicians should maintain a high index of suspicion for bullous Kaposi sarcoma in elderly individuals with blistering lesions, enabling timely diagnosis and appropriate management. Further studies are warranted to improve our knowledge of this rare variant and enhance treatment approaches.

**References**

Glibenclamide-induced Photoallergic Reaction

Eva Rupert Gostiša¹, Ružica Jurakić Tončić¹, Stefano Caccavale², Romana Čeović¹

¹ Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia
² Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy

Citation: Rupert Gostiša E, Jurakić Tončić R, Caccavale S, Čeović R. Glibenclamide - Induced Photoallergic Reaction. Dermatol Pract Concept. 2024;14(2):e2024114. DOI: https://doi.org/10.5826/dpc.1402a114
Accepted: November 14, 2023; Published: April 2024
Copyright: ©2024 Rupert Gostiša et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.
Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
Corresponding Author: Professor Romana Čeović, MD, PhD, Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia. E-mail: romana.ceovic@gmail.com

Case Presentation

A 78-year-old female with psoriasis came to our department due to PUVA phototherapy. Following five PUVA sessions (each exposure of 5 J/cm²), a reaction occurred presenting as intense erythema, followed by lamellar desquamation. According to the data, she had been exposed to the sun every summer during the last 20 years and had had several previous PUVA treatments for psoriasis but had not experienced any kind of skin reaction or sun intolerance. The only medication she had been taking was glibenclamide for the past 20 years. When the reaction occurred, she was treated with parenteral dexamethasone of 8 mg for three consecutive days, followed by oral prednisone 30 mg for five days, 20 mg for five days, and 10 mg for five days as well with topical corticosteroids. She was advised to stop taking glibenclamide and to avoid all other types of sulfonylurea drugs. Avoidance of sunlight, protective clothing, and application of broadband sunscreen with UVA filters were recommended. Patch test and photo patch test to glibenclamide with exposure to 5 J of UVA were done. Despite negative results, glibenclamide was substituted with metformin, and symptoms gradually diminished within the following few weeks, without post-inflammatory hyperpigmentation.

Teaching Point

Photoallergic reaction is a cell-mediated type IV hypersensitivity that occurs due to interaction between the chemical photosensitizer and subsequent exposure to UV radiation, mostly UVA. The reaction is dose-independent, requires prior sensitization, and usually develops days/months after the exposure, sometimes even years [1]. Drugs constitute a major group of photosensitizers. Glibenclamide is a sulfonylurea hypoglycemic drug used for the treatment of type II diabetes [2]. Even though in our patient’s photopatch test to glibenclamide was negative, symptoms disappeared within a short time after glibenclamide withdrawal and avoidance of UVA radiation. This identified glibenclamide as the culprit drug and suggested the diagnosis of photoallergic reaction. Physicians should be aware that glibenclamide-induced photoallergic reaction can develop many years after starting the medication; taking detailed medical history of a patient is therefore very important.
References


*Figure 1. (A, B) Development of intense erythema with lamellar desquamation on the face, neck, and upper extremities after long-term glibenclamide use and subsequent exposure to phototherapy.*
Dermoscopic Findings in Skin Infection by Mycobacterium Immunogenum

José Magna Aguirre¹, Paula Almeida Abarcia¹, Pablo Vargas Mora¹

¹ Dermatology Department, Facultad de Medicina, Universidad de Chile, Santiago, Chile

Case Presentation

A 34-year-old female patient, with no relevant medical history, presented with a painful lesion on her right buttock, accompanied by transparent discharge. This lesion had appeared two weeks after receiving an intramuscular injection of a “cell regeneration product” at the injection site. Examination revealed a 2 cm orange nodule with well-defined borders and whitish areas inside, above an 4 cm erythematous-violaceous plaque (Figure 1A). Dermoscopy revealed a yellowish-orange lesion with thick whitish structures inside and polymorphic vessels (linear irregular, hairpin and comma vessels). It was surrounded by a milky-red area with poorly defined edges (Figure 1B). Biopsy and culture of the lesion were performed. Mycobacterium immunogenum was isolated, and it was decided to start antibiotics.

Teaching Point

Dermoscopic findings in skin infections by Mycobacterium tuberculosis and Mycobacterium leprae have already been described in the literature; however, the available information for atypical mycobacteria is limited to two publications to date [1]. In this case, we observed some dermoscopic findings similar to those described in the literature for other mycobacteria: orange-yellowish areas, whitish structures, and vessels of varying morphology [1]. It is important to consider that the lack of orange areas does not rule out...
Figure 1. (A) 2 cm orange nodule with well-defined borders and whitish areas inside, above an approximately 4 cm erythematous-violaceous plaque. (B) Yellowish-orange lesion with well-defined borders, with thick whitish structures inside and the presence of polymorphic vessels.

granulomatous infection [2]. This is the first case report in the literature to mention dermoscopic findings in a Mycobacterium immunogenum infection. Therefore, a high index of suspicion for mycobacterial infection should be maintained in the presence of these dermoscopic findings, along with a suggestive medical history, which can guide the diagnostic process toward reaching a microbiological diagnosis.

References
A Nodular Melanoma Mimicking a Blue Nevus: A Case Report

Giovanni Marco D’Agostino¹, Tommaso Bianchelli¹, Giulia Veronesi¹, Valentina Di Gregorio¹, Donatella Brancorsini²

¹Dermatology Unit, Istituto Nazionale di Riposo e Cur a per Anziani, INRCA-IRCCS Hospital, Ancona, Italy
²Institute of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region, Ancona, Italy

Citation: D’Agostino GM, Bianchelli T, Veronesi G, Di Gregorio V, Brancorsini D. A Nodular Melanoma Mimicking a Blue Nevus a Case Report. Dermatol Pract Concept. 2024;14(2):e2024116. DOI: https://doi.org/10.5826/dpc.1402a116

Accepted: December 10, 2023; Published: April 2024

Copyright: ©2024 D’Agostino et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. G.M. D’Agostino and T. Bianchelli equally contributed to the manuscript.

Corresponding Author: D’Agostino Giovanni Marco, MD, Dermatological Unit, INRCA Ancona, Via della Montagnola 81, 60127, Ancona, Italy. Email: giovannimarcodagostino@gmail.com

Case Presentation

A 77-year-old female presented to our clinic for a routine consultation.

The examination showed at the right temporal region of the scalp a nodular lesion reported as having been present for many years and clinically described as a blue nevus but recently enlarged in volume. The lesion was excised, dermoscopy showed aspects compatible with a blue nevus (Figure 1).

The diagnosis was nodular melanoma with Breslow of 4 mm. Both sentinel lymph node and total body computed tomography (TBCT) were negative, and the patient is in six-month clinical and instrumental follow-up.

Teaching Point

Blue nevus is a benign melanocytic lesion that rarely undergoes malignant changes.

Melanoma rarely originates on blue nevi, and many of the reported cases are cellular blue nevi with lymph nodes containing nevi cells.

There is no consensus about which prognostic indicators predictive of outcome in conventional malignant melanoma are applicable to blue nevus-like melanoma/blue nevus-associated melanoma, and the biological behavior of these lesions is not always predictable.

It is critical to focus on the story of rapid size increase even of lesions with reassuring clinical and dermoscopic aspects.
References


Case Presentation

A 33-year-old male, recently returned from a trip to Argentina, was admitted with an ulcer on the left temple, erythematous oedema of the left eyelid, ulcer on the left cheek (Figure 1 A, B), and left preauricular and laterocervical lymphadenopathy. The patient complained of fever (≤38.4°C), headache, arthralgia, and myalgia. A diagnosis of ecthyma gangrenosum was made. Bacteriological examination was positive for *Staphylococcus aureus*. Laboratory tests showed leukocytosis with lymphocytosis and increased erythrocyte sedimentation rate and C-reactive protein. According to antibiogram results, the patient was treated with i.m. ceftriaxone (2 g/day for 10 days). He was seen again two weeks later; however, all symptoms persisted. We then remembered the patient’s trip to Argentina, and a diagnosis of Chagas disease (American trypanosomiasis) was hypothesized. Indirect immunofluorescence and ELISA test were positive for *Trypanosoma cruzi* infection. The patient was treated with oral benznidazole (375 mg/day for two months). Complete remission was observed six weeks later. Two-year follow-up was negative.

Teaching Point

Chagas disease is caused by protozoan *Trypanosoma cruzi*. It is endemic in Central and South America. It is usually transmitted by feces of bedbugs of the subfamilies Reduviidae and Triatominae, in particular *Triatoma infestans*. Reservoirs are wild animals and humans. However, Chagas disease can be transmitted also by blood transfusion, solid organ transplant, and food contaminated by feces of the bedbugs. Acute Chagas disease is characterized by fever, arthralgia, myalgia, and Romaña sign (unilateral erythematous oedema, conjunctivitis, and preauricular lymphadenitis). Benznidazole and nifurtimox are the drugs of choice [1,2].
References


Figure 1. (A, B) Ulcer located on the left temple, erythematous edema of the left eyelid, and ulcer on the left cheek.
Nilotinib Induced Keratosis Pilaris in a Female with Chronic Myeloid Leukemia

Ranjana Beniwal¹, Akriti Agrawal²

¹ Dr. Sampurnanand Medical College and associated group of hospitals, Jodhpur, India
² Department of Dermatology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

Case Presentation

A 34-year old female on nilotinib 200 mg twice daily for chronic myeloid leukemia presented with multiple asymptomatic gradually progressive raised lesions over body for four years. She was not on any other medications and developed the lesions a few weeks after starting nilotinib. Examination revealed skin-colored-to-erythematous follicular hyperkeratotic papules over face, trunk, and bilateral upper and lower limbs. Routine investigations were within normal limits. Histopathology showed orthokeratosis, follicular plugging with perifollicular fibrosis, and a mild lymphocytic inflammatory infiltrate. Based on temporal correlation with drug intake and inexplicability of occurrence of the eruption due to disease or other drugs, it was diagnosed as a case of nilotinib-induced keratosis pilaris.

Teaching Point

Nilotinib is a second-generation BCR-ABL tyrosine kinase inhibitor (TKI) [1]. The various cutaneous adverse effects of TKIs include alopecia, xerosis, maculopapular rash, photosensitivity, hypopigmentation, and edema. Keratosis pilaris-like eruption has been reported with the more potent second and third generation multitranslated TKIs like nilotinib, dasatinib, and posatinib and is attributed to their expanded spectrum of activity against related kinase targets other than BCR-ABL [2]. The rash is usually asymptomatic
or pruritic and characterized by a generalized distribution on the face, trunk, and extremities. It typically starts several weeks after initiation of the drug and is not dose-dependent. Currently, there is no consensus regarding treatment of keratosis pilaris-like eruption induced by nilotinib. The rash is usually refractory to treatment in the majority of cases and may resolve partially or completely after withdrawal of the treatment.

**References**


Vulvar Acantholytic Warty Dyskeratoma

Sabina Vaccari¹, Luca Rapparini¹², Cosimo Misciali¹², Emi Dika¹²

¹ Oncologic Dermatology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy
² Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Italy

Case Presentation

A 43-year-old female was examined for an exophytic nodule on the internal side of the small vulvar lip (Figure 1A). She referred the occurrence for 25 years.

On clinical examination, the lesion appeared as a well-circumscribed pinkish nodule, with a central umbilicated crater filled with keratin. On dermoscopy, a smooth surface of the lesion, color of the surrounding mucosa, on the periphery is appreciated. In the central area an accumulation of whitish keratotic scales overlying a verrucous-papillary surface with linear and corkscrew-shaped vessels was observed (Figure 1B).

Condyloma, squamous cell carcinoma, and keratoacanthoma were hypothesized clinical differential diagnoses, so it was decided to proceed with a radical excision.

On histopathologic evaluation, there is well-circumscribed neoplasm with invagination of marked epidermis hyperplasia with columns of parakeratosis, dyskeratotic acantholysis containing round keratinocytes separated from one another. Edema, dilated vessels in the superficial chorion (Fig. 1C, D).

The histological investigations concluded for acantholytic warty dyskeratoma.

Teaching Point

Acantholytic warty dyskeratoma is an uncommon benign epidermal proliferation which can involve both the skin and the mucous membranes, in particular the oral mucosa, the pharynx, the perineum, the rectal mucosa, and the vulva [1]. It should be included within the spectrum of dermatoses with focal acantholytic dyskeratosis. Histologically, it is characterized by a crater-shaped epidermal proliferation with prominent dyskeratosis, acantholysis, superimposed by parakeratotic cells, with edema and dilated vessels in the superficial chorion. These histological findings allow the diagnosis of acantholytic warty dyskeratosis and rule out other common conditions affecting the vulvar region [2].
Figure 1. Well-circumscribed pinkish nodule, with a central umbilicated crater filled with keratin (A). A smooth surface of the lesion, color of the surrounding mucosa on the periphery, and an accumulation of whitish keratotic scales overlying a verrucous-papillary surface, with linear and corkscrew-shaped vessels in the central area (B). Well-circumscribed neoplasm with invagination (H&E, 4x) (C) and column of parakeratosis, dyskeratotic acantholysis containing round keratinocytes separated from one another (H&E, 25x)(D).

References

Pigmented Eccrine Poroma on the Palm Mimicking Nodular Melanoma

Inghlide Damanielle Silva¹, João Paulo Monteiro Yamagata¹, Thales Pereira de Azevedo¹, Maria Auxiliadora Jeunon Sousa², Thiago Jeunon de Sousa Vargas²

¹ Yamagata Dermatology Clinic, Rio de Janeiro, Brazil
² Laboratory ID – Investigação em Dermatologia, Rio de Janeiro, Brazil

Case Presentation
A 48-year-old male presented with a growing brownish papule over the preceding three months on the left palm, where he reported a previously existing pigmented lesion. On physical examination, he displayed a smooth-surfaced, brownish papule measuring 2 mm in diameter (Figure 1A). Dermoscopic examination revealed a poorly defined brown network, erythema, and a grayish-blue veil (Figure 1B). The lesion was excised under local anesthesia and sent for histopathological examination, which showed columns of poroid cells in continuity with the base of the epidermis and extending to the superficial dermis (Figure 1C). A closer examination revealed cuticular cells with abundant eosinophilic cytoplasm and an eosinophilic cuticle lining the glandular duct (Figure 1D). Melanin was identified in the cytoplasm of the cells, and melanocytes without forming nests among poroid cells were seen (Figures 1E, 1F). These findings were crucial in ruling out melanoma and confirming the diagnosis of pigmented eccrine poroma (PEP).

Teaching Point
Eccrine poromas represent 10% of sweat gland tumors, arising in the intraepidermal section of eccrine sweat ducts [2]. Rarely pigmented, the brownish coloration arises from scattered dendritic melanocytes within tumor cells [1]. There is no consensus on the dermoscopic features of PEP. Structures like streaks, a white-blue veil, and dermatoscopic structures suggestive of regression, common in melanoma, have been observed in the histological variant with an epidermal component. This complicates an already uncommon diagnosis, potentially causing confusion with other pigmented tumors like melanoma, pigmented basal cell carcinoma, and Bednar tumor [2]. Therefore, histopathological examination is essential for confirming the diagnosis.
References


Figure 1. (A) Brownish papule on the left palm. (B) Dermoscopy reveals a poorly defined brown network, erythema, and a grayish blue veil. (C) Histological examination shows columns of poroid cells in continuity with the epidermis and extending to the superficial dermis. (H&E, x20). (D) Poroid cells intermingle with a smaller number of cuticular cells with abundant eosinophilic cytoplasm around a small duct lumen with debris (H&E, x400). (E) Abundant melanin was found in the cytoplasm of poroid cells (Fontana-Masson, x400). (F) Several dendritic single melanocytes were found between poroid cells (MELAN-A, x200).
Trichomycosis Axillaris: An Underdiagnosed Hair Shaft Condition

Juan Manuel Liñán Barroso¹, Norberto Sánchez Rodríguez²

1 Dermatology Department. Trichology Unit. Virgen del Rocío University Hospital, Seville, Spain
2 Neurology Department. Virgen del Rocío University Hospital, Seville, Spain

Citation: Liñán Barroso JM, Sánchez Rodríguez N. Trichomycosis Axillaris: An Underdiagnosed Hair Shaft Condition. Dermatol Pract Concept. 2024;14(2):e2024134. DOI: https://doi.org/10.5826/dpc.1402a134

Accepted: December 12, 2023; Published: April 2024

Copyright: ©2024 Liñán Barroso et al. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (BY-NC-4.0), https://creativecommons.org/licenses/by-nc/4.0/, which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Juan Manuel Liñán Barroso, MD, Dermatology Department, Virgen del Rocío University Hospital, Manuel Siurot Avenue s/n, Seville, Seville (Spain), 41013. ORCID: 0000-0002-6023-3151; Telephone number: +34/955013057; E-mail: juanm.linan.sspa@juntadeandalucia.es

Case Presentation

A 27-year-old male patient with a history of hidradenitis suppurativa and hyperhidrosis presented with an anomalous appearance and fragility of bilateral axillary hair for five years, without involvement of other regions, which did not respond to treatment with sertaconazole cream. On physical examination, there was axillary hair with devitalized appearance and positive pull and tug tests. Dermoscopy revealed white-yellowish lumpy sheath-like masses attached to the hair shaft. Wood’s light showed intense white color in the affected hair. Microscopic analysis confirmed the presence of mucoid sheaths around the hair and colonization of the hair shafts by gram-positive cocobacilli. Fungal culture was negative. The definitive diagnosis was trichomycosis axillaris caused by Corynebacterium flavescent, which resolved after one week of treatment with clindamycin gel.

Figure 1. Trichoscopy showing white-yellowish lumpy sheath-like masses attached to the hair shaft.
Teaching Point

Trichomycosis axillaris is an underdiagnosed condition that commonly affects the axillary region [1]. It should be considered in the differential diagnosis in cases of abnormal appearance of the hair shaft.

References