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Diagnosis and Differential Diagnosis of Poikiloderma of Civatte: A Dermoscopy Cohort Study

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Key words: poikiloderma, dermoscopy, epidemiology, diagnosis, differential diagnosis

Citation: Katoulis AC, Sgouros D, Bozi E, et al. Diagnosis and differential diagnosis of Poikiloderma of Civatte: a Dermoscopy Cohort Study. Dermatol Pract Concept. 2023;13(1):e202307. DOI: https://doi.org/10.5826/dpc.1301a7

Accepted: July 15, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Poikiloderma of Civatte (PC) is a common, acquired, chronic, benign poikiloderma of the neck and face, most commonly affecting peri-menopausal females. At the time of writing, few studies have been published regarding the dermoscopy of PC.

Objective: To describe the dermoscopic picture of PC, so as to provide a clinico-dermoscopic diagnosis and differential diagnosis for PC.

Methods: Twenty-eight patients with PC, aged 26-73 years, of whom 19 females (67.86%) were evaluated by detailed history, clinical examination, and dermoscopic examination with hand-held dermoscope.

Results: The reticular pattern was observed in 15 cases (53.6%); the white dot in 10 (35.7%); the non-specific in 9 (32.1%); and the combination of linear and dotted vessels in 8 (28.6%). Regarding local dermoscopic features, converging curved vessels were observed in 18 cases (64.3%); linear irregular vessels in 17 (60.7%); rhomboidal/polygonal vessels in 15 (53.6%); dotted/globular vessels in 10 (35.7%); white macules in 23 (82.1%); brown macules in 11 (39.3%); and whitish follicular plugs in 6 (21.4%).

Conclusions: The dermoscopic picture of PC is highly characteristic and corresponds well to both clinical and histological findings. Dermoscopy may assist clinical diagnosis, as well as the differentiation from other dermatoses of the neck and face, especially poikilodermas with guarded prognosis.
Introduction

Poikiloderma of Civatte (PC) is a rather common benign dermatosis of the neck and face, mainly affecting fair-skinned individuals, especially postmenopausal females. It is characterized by a combination of a reticular pattern of linear telangiectasia, mottled hyperpigmentation and superficial atrophy [1,2]. Clinically, it involves symmetrically sun-exposed areas of the face, the neck, and the V-shaped area of the chest, invariably sparing the anatomically shaded areas [1,2]. Depending on the prevalent clinical feature, PC can be classified into erythematotelangiectatic, pigmented, and mixed clinical types [2]. The etiopathogenesis of PC is incompletely understood. Exposure to ultraviolet radiation, hormonal changes of menopause, contact sensitization to perfumes and cosmetics, and normal ageing have been incriminated. The diagnosis is usually clinical and can be confirmed by histology, which is characteristic, but not pathognomonic [3]. The course is slowly progressive and irreversible, often causing significant cosmetic disfigurement.

Dermoscopy is an in vivo diagnostic technique that has considerably increased our diagnostic skills. Its use has been extended, apart from Dermato-oncology, in almost every disease in the context of General Dermatology [4-6]. At the time of writing, very few studies have been published regarding the dermoscopy of PC.

Objectives

The aim of the present study was to describe the dermoscopic picture of PC. Furthermore, we sought to assist the differentiation of PC from other dermatoses of the face and neck and most importantly from acquired poikilodermas with poor or guarded prognosis (poikiloderma vasculare atrophicans and poikiloderma associated with collagen vasculopathy), thus reducing the need for biopsy and histologic verification [1,2].

Material and Methods

The study was conducted at the 2nd Department of Dermatology and Venereology of the National and Kapodistrian University of Athens at “Attikon” General University Hospital in Athens, Greece during a period of 18 months (January 2018 – June 2019). Patients with a clinical diagnosis of PC, visiting the outpatient clinic of our department, were recruited after they had given their informed consent. The study was approved by the Ethics Committee of the Hospital.

In all patients, a detailed history was obtained which included: demographic characteristics; family history with an emphasis on the presence of a similar condition in other family members; medical history, including drug history; in females, gynecological history and menstrual status; skin phototype according to Fitzpatrick’s classification; sun exposure habits: occupational or recreational, and the level of exposure; use of sunscreens; use of fragrances or fragranced cosmetics, applied on the sides of the neck or the décolleté area of the chest; and history of PC.

During clinical examination, the following clinical parameters were recorded: location; distribution; clinical type; and presence of clinical manifestations of rosacea. The dermoscopic examination was performed by an experienced evaluator (A.C.K.). For the dermoscopic examination, a DermLite DL200Hybrid (3Gen, San Juan Capistrano CA, USA) hand-held dermoscope was used. Examination employed polarized light and a 10-fold magnification either without contact of the glass slide with the skin or with contact but without applying pressure on the skin (for better visualization of the vascular component). Photographic documentation was made using an iPhone 8 camera. Photographs were taken from seven preselected sites, the same for all patients, on the upper chest, the sides of the neck, and the peripheral face in a symmetrical manner.

Firstly, we attempted to describe the local features, pigmented or vascular, that predominated on dermoscopic examination among our patients. The following structures were assessed: (i) rhomboidal/polygonal vessels, (ii) linear irregular vessels, (iii) dotted/globular vessels, (iv) brown macules, (v) white macules, (vi) follicular plugs. Secondly, we analyzed and described the global pattern.

Statistical Methods

For continuous variables, the mean, standard deviation and range, or the median, 25th and 75th percentiles and range, were used after testing for normal distribution. For categorical variables, the frequencies and percentages were used. The Shapiro-Wilk test for normality was applied.

Chi-squared and Fischer’s exact tests were used for the comparison of categorical variables while unpaired t-tests and Mann-Whitney U tests were applied depending on the distributions of the continuous variables. All statistical analyses were performed using Stata/IC version 15.

Results

The demographics, etiologic factors and clinical characteristics of our patients are summarized in Table 1. In total, 28 patients with PC were recruited. The median age was 55 years (range 26-73 years). There were 19 females (67.86%) aged 46-73 years (median age 54 years), and 9 males aged 26-65 years (median age 59 years).

On clinical examination, the mixed type was the most prominent (71.43%), followed by the erythematotelangiectatic type (21.43%) and the pigmented type (7.14%). The
most common localization was the V-shaped area of the chest. Less than one-third of the patients complained of accompanying symptoms (burning, flushing and pruritus).

The most commonly reported comorbid skin condition was rosacea (mainly of the erythemato-telangiectatic type), observed in approximately half of the patients. Moreover, disorders of the thyroid gland were also common, involving 28.57% of the patients. It is of interest that 4/28 cases (14.28%) had a history of systemic lupus erythematosus.

On dermoscopic examination, the local dermoscopic features were assessed. We observed linear irregular vessels in 17 cases (60.7%); rhomboidal/polygonal vessels in 15 cases (53.6%); dotted/globular vessels in 15 cases (53.6%); white macules in 23 cases (82.1%); brown macules in 11 cases (39.3%); and whitish follicular plugs in 6 cases (21.4%). In 18 cases (64.3%), we identified a distinctive type of vessels, the converging curved vessels, presenting as two curved red lines that meet at their neighboring end, giving the impression of a flock of seagulls flying with their wings wide open ("flying-seagull-like" vessels). Examples of the local dermoscopic features observed among patients with PC are shown in Figure 1.

Based on the presence of the aforementioned vessel types and their architectural distribution, we described four patterns:

- Reticular (fishnet-like) pattern: areas with linear telangiectasias that are interconnected forming an irregular red network that is reminiscent of a fishnet. This network consists of thin red lines and quadrilateral or polygonal, irregular openings.
- White dot (red-white polka dot) pattern: white roundish macules, regularly distributed in areas of bright red erythema produced by a network of linear telangiectasias. It is reminiscent of a red-white polka dot print.
- Combination of linear and dotted vessels pattern: a combination of linear irregular vessels and dotted/globular vessels. This pattern was initially described in patients with PC by Errichetti and Stingo as “spaghetti and meatballs” pattern.\(^7\)
- Non-specific pattern: areas of irregular linear telangiectasias that are irregularly distributed and do not correspond to any specific pattern.

The dermoscopic global patterns are summarized in Table 2. The reticular pattern was observed in more than

### Table 1. Demographics, etiologic factors and clinical characteristics of the patients with PC (N=28).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>19 (67.86)</td>
<td>9 (32.14)</td>
</tr>
<tr>
<td>Age</td>
<td>55 years</td>
<td>59 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiologic factors</th>
<th>Phototype (Fitzpatrick’s classification)</th>
<th>Occupational sun exposure</th>
<th>Recreational sun exposure</th>
<th>Sunburn in childhood</th>
<th>Use of perfumes</th>
<th>Menopause</th>
<th>Positive family history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>3 (10.71)</td>
<td>22 (78.57)</td>
<td>2 (7.14)</td>
<td>16 (57.14)</td>
<td>13 (68.42)</td>
<td>9 (32.14)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>7 (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>14 (50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>4 (14.29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Duration</th>
<th>Location of the lesions</th>
<th>Clinical type</th>
<th>Symptoms</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-5 years</td>
<td>V-shaped area of chest:</td>
<td>Erythemato-telangiectatic:</td>
<td>Burning:</td>
<td>Rosacea</td>
</tr>
<tr>
<td></td>
<td>6-10 years</td>
<td>Sides of the neck:</td>
<td>Pigmented:</td>
<td>Flushing:</td>
<td>Thyroid diseases</td>
</tr>
<tr>
<td></td>
<td>11-15 years</td>
<td>Peripheral face:</td>
<td>Mixed:</td>
<td>Pruritus:</td>
<td>Arterial hypertension:</td>
</tr>
<tr>
<td></td>
<td>16-20 years</td>
<td></td>
<td></td>
<td></td>
<td>Systemic lupus erythematosus:</td>
</tr>
<tr>
<td></td>
<td>5 (17.86)</td>
<td>27 (96.43)</td>
<td>6 (21.43)</td>
<td>8 (28.57)</td>
<td>12 (42.8)</td>
</tr>
<tr>
<td></td>
<td>11 (39.29)</td>
<td>11 (39.29)</td>
<td>2 (7.14)</td>
<td>6 (21.42)</td>
<td>8 (28.57)</td>
</tr>
<tr>
<td></td>
<td>9 (32.14)</td>
<td>8 (28.57)</td>
<td>20 (71.43)</td>
<td>5 (17.85)</td>
<td>5 (17.85)</td>
</tr>
<tr>
<td></td>
<td>3 (10.71)</td>
<td>8 (28.57)</td>
<td></td>
<td>4 (14.28)</td>
<td>4 (14.28)</td>
</tr>
</tbody>
</table>

Numbers in parenthesis represent percentages.
Figure 1. “Local structures of poikiloderma of Civatte”. A) The rhomboidal/polygonal vessels, B) the converging curved vessels, C) the dotted/globular vessels, D) the linear irregular vessels, E) the white macules, F) the brown macules, and G) the follicular plugs.

Table 2. Dermoscopic features in patients with PC (N=28).

<table>
<thead>
<tr>
<th>Dermoscopic patterns/structures</th>
<th>Description</th>
<th>Number of patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticular (fishnet-like)</td>
<td>Areas with linear telangiectasias that are interconnected forming an irregular red network that is reminiscent of a fishnet. This network consists of thin red lines and quadrilateral or polygonal, irregular openings.</td>
<td>15 (53.57)</td>
</tr>
<tr>
<td>White dot (red-white polka dot)</td>
<td>Areas of bright red erythema produced by a network of linear telangiectasias, surrounding regularly distributed white roundish macules. It is reminiscent of a red-white polka dot print.</td>
<td>10 (35.71)</td>
</tr>
<tr>
<td>Combination of linear and dotted vessels (spaghetti and meatballs-like)</td>
<td>A combination of linear irregular vessels and dotted/globular vessels.</td>
<td>4 (14.28)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>Areas of linear telangiectasias that are irregularly distributed and do not correspond to any specific pattern.</td>
<td>9 (32.14)</td>
</tr>
<tr>
<td>Vascular structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhomboidal/polygonal</td>
<td>Bright red, non-branching, linear telangiectatic vessels; tend to connect with surrounding vessels forming interconnected rhomboidal or polygonal vascular structures, thus resembling parts of fishnet with irregular holes.</td>
<td>15 (53.57)</td>
</tr>
<tr>
<td>Linear irregular</td>
<td>Bright red, non-branching, linear telangiectasias with irregular form and distribution.</td>
<td>17 (60.71)</td>
</tr>
<tr>
<td>Dotted/globular</td>
<td>Bright red, irregularly distributed dots or globules.</td>
<td>10 (35.71)</td>
</tr>
</tbody>
</table>
In our statistical analysis, we investigated possible correlations of the dermoscopic features and patterns with epidemiologic parameters, etiologic factors and clinical characteristics of our PC patients (Table 4). The following statistical correlations were documented: white macules were correlated with the mixed clinical type ($p=0.015$); converging curved vessels were correlated with the erythematotelangiectatic type ($p=0.028$); brown macules were associated with skin phototype IV ($p=0.016$) and with disease duration.

### Table 3. Dermoscopic differential diagnosis of poikiloderma of Civatte.$^{11-23}$

<table>
<thead>
<tr>
<th>Dermoscopic patterns/structures</th>
<th>Description</th>
<th>Number of patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Converging curved vessels (Flying seagull-like)</td>
<td>Double curved short red lines that meet at their neighboring end; usually appear in small clusters.</td>
<td>18 (64.29)</td>
</tr>
<tr>
<td>Pigmented structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown macules</td>
<td>Light brown structureless macules, 2-3 mm in diameter, with rather distinct but slightly irregular borders.</td>
<td>11 (39.29)</td>
</tr>
<tr>
<td>Depigmented structures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White macules</td>
<td>Whitish or skin-colored spots, suggesting that they correspond to the holes of the vascular network which is formed by the linear telangiectasias, representing areas of sparing.</td>
<td>23 (82.14)</td>
</tr>
<tr>
<td>White keratotic follicular plugs</td>
<td>Follicular hyperkeratosis</td>
<td>6 (21.42)</td>
</tr>
</tbody>
</table>

- **Dermoscopic findings**
  - **Riehl’s Melanosis**
    - Gray dots/granules and pigmented pseudo-network, combined with telangiectatic vessels;
    - Less often flour-like scales, follicular keratotic plugs and perifollicular whitish halo.
  - **Erythromelanosis follicularis faciei et colli**
    - Round whitish areas with follicular plugs, occasionally centered by a hair;
    - Surrounding blue-gray dots or peppering in a reddish-brown background
  - **Poikiloderm in dermatomyositis**
    - Enlarged linear irregular vessels;
    - Mixed features of hyperpigmentation and depigmentation.
  - **Poikilodermatous mycosis fungoides**
    - Multiple polygonal structures consisting of lobules of white storiform streaks, studded with fine red dots or hairpin vessels;
    - Unevenly and intermittently distributed septa of pigmented dots, between the lobules;
    - Red and yellowish smudges.
  - **Poikiloderma atrophicans et vasculare**
    - Blurred branched vessels on a reddish or orangish-brown background;
    - Sparse whitish scales.
  - **Chronic Graft-versus-host disease**
    - Whitish scales;
    - Vessels of mixed morphology, mostly dotted and linear
  - **Melasma**
    - Light-to-dark brown background;
    - Brown granules/globules with perifollicular sparing;
    - Global reticular or pseudo- reticular pattern.

Half of the patients, followed by the white dot pattern, and the non-specific pattern, while the combination of linear and dotted vessels pattern was the least frequently identified. In 78.57% of the cases, the coexistence of more than one pattern at different sites was noted. When the global pattern was assessed by anatomic region, i.e. face, neck, and upper chest, no significant differences were observed. Examples of the dermoscopic global patterns observed among our patients are shown in Figure 2.
Table 4. Distribution of local dermoscopic features by clinical type among patients (N=28) with poikiloderma of Civatte.

<table>
<thead>
<tr>
<th>Type of PC Dermoscopic Features</th>
<th>Erythemato-telangiectatic type (N=6)</th>
<th>Pigmented type (N=2)</th>
<th>Mixed type (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhomboidal/polygonal vessels</td>
<td>2 (33.33)</td>
<td>0</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Dotted/globular vessels</td>
<td>4 (66.66)</td>
<td>1 (50)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Linear irregular vessels</td>
<td>3 (50)</td>
<td>2 (100)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Converging curved vessels</td>
<td>6 (100)</td>
<td>1 (50)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>White macules</td>
<td>3 (50)</td>
<td>1 (50)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Brown macules</td>
<td>1 (16.67)</td>
<td>2 (100)</td>
<td>9 (45)</td>
</tr>
</tbody>
</table>

Figure 2. “Global patterns of poikiloderma of Civatte”. A) The fishnet-like pattern, B) the red-white polka dot pattern, C) the combination of linear & dotted vessels pattern, and D) the non-specific pattern.
>5 years (p=0.009). Nevertheless, the number of cases in our study was relatively small to allow the extrapolation of solid conclusions.

Conclusions

As our results indicate, PC exhibits a rather characteristic dermoscopic picture. The dermoscopic findings in PC consist of vascular and pigmented local features, forming a reddish-to-brownish network. We were able to describe four distinct global patterns (reticular, white dot, combination of linear and dotted vessels, and non-specific). The reticular pattern was the most frequently identified (53.57%). In the majority of patients, the coexistence of more than one pattern was noted. We were able to describe four types of telangiectatic vessels (converging curved, rhomboidal/polygonal, dotted/globular, and linear irregular). Converging curved vessels have not been described previously in any skin condition and could be considered highly characteristic of the erythematotelangiectatic type of PC (p=0.028). White macules were seen in the vast majority of our patients and in all clinical types, either regularly (white dot pattern) or irregularly (reticular or non-specific pattern) distributed and in a follicular or pseudo-follicular distribution. Brown macules were observed much less often, mostly associated with the pigmented and the mixed clinical type.

In the literature, there is little published experience on the dermoscopy of PC. Errichetti and Stinco studied 8 consecutive cases (6 women and 2 men, aged 42–73 years, mean 51 years) of clinically diagnosed PC. The authors described, in all patients, a combination of dotted/globular vessels and linear irregular vessels, giving the impression of “spaghetti and meatballs”, along with perifollicular whitish (spared) areas. In addition, they noted the presence of follicular keratotic plugs and delicate reticular or structureless brownish areas in 25% and 12.5% of the cases, respectively. Our findings are in line with the findings of Errichetti and Stinco. However, the combination of linear and dotted vessels pattern was not recognized by us as the predominant global pattern, but it was seen in as much as 28.6% of our patients. The presence of dotted/globular vessels was less common in our cohort as well. Accordingly, for the white macules, we noticed that they often have a pseudo-follicular distribution, i.e. they are not strictly related to the follicular openings. In our cohort, brown macules were mainly associated with skin phenotype IV (p=0.016) and with a disease duration >5 years (p=0.009). Brown macules were mostly identified in the pigmented and mixed clinical types of PC.

The dermoscopic findings correlate well with both the clinical and histologic features of PC, supporting the view that dermoscopy represents a bridge between clinical presentation and histology. The vascular dermoscopic structures (converging curved vessels, rhomboidal/polygonal vessels, linear irregular vessels, dotted/globular vessels) that we identified are the dermoscopic correlates of linear telangiectasia of poikiloderma and represent the dilated hyperemic vessels of the papillary dermis that have been described in the histopathology of PC. When the course of the vessels is parallel to the skin surface, they appear on dermoscopy as rhomboidal/polygonal or linear irregular vessels, while when their course is perpendicular they appear as dotted/globular vessels. The mottled hyperpigmentation of poikiloderma is dermoscopically appreciated as brown macules, and results from the increased presence of melanin irregularly distributed in the basal layer of the epidermis, as well as the presence of melanophages laden with melanin in the dermis. In our series, brown macules correlated with the mixed type of PC (p=0.015). White macules correspond to the superficial atrophy that integrates the clinical triad of poikiloderma. White macules correlate histologically to a flattened and atrophic epidermis, overlying an elastic papillary dermis at sites in between the reticulate telangiectasia.

PC presents with a distinctive dermoscopic picture. By dermoscopy, PC can be easily differentiated from other skin conditions characterized also by telangiectasia and reticular pigmentation, such as rosacea, erythromelanosis follicularis faciei et colli and melasma, or true poikiloderma. Rosacea which often coexists with PC most commonly involves the central face. In rosacea, linear telangiectatic vessels arranged in horizontal and vertical lines form polygons (polygonal vessels) and vascular polygons are a characteristic dermoscopic feature of erythematotelangiectatic rosacea. The vascular polygons are similar to the polygonal vessels observed in half of our patients with PC, providing further support to the theory that rosacea and PC are related and, possibly, belong to the same nosological spectrum. In rosacea, additional features such as rosettes, white/yellowish scales, orange-yellowish areas, pigmentation structures, dilated follicles and follicular pustules (in the papulopustular form), have been described that were not present in our cohort allowing differentiation between these entities. The dermoscopic differential diagnosis of PC is depicted in Table 3.

Our study has several limitations. Due to the small number of patients, our results need further confirmation in larger prospective cohorts. Additionally, due to the lack of a control group, the sensitivity and specificity of the proposed criteria were not calculated.

To our knowledge, this is the first study to systematically investigate the dermoscopic characteristics of PC. Although not pathognomonic, the dermoscopic picture is highly characteristic, leading to the clinical diagnosis with great confidence. We were able to describe patterns and features that are unique for PC, permitting the differentiation from other
dermatoses of the face and neck, as well as from other forms of poikiloderma with guarded or serious prognosis. Dermoscopic findings correlate well with the clinical and histological features of PC. On this basis, biopsy and histologic examination are rarely necessary. Future research will, hopefully, better clarify the pathogenetic mechanisms of this disease and will provide insights for more effective preventive and therapeutic approaches for PC.

References

Lip Mesotherapy with Dexpanthenol as a Novel Approach to Prevent Isotretinoin-Associated Cheilitis

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Key words: cheilitis, dexpanthenol, isotretinoin, mesotherapy, mucocutaneous side effect

Citation: Turan Ç, Öner U. Lip mesotherapy with dexpanthenol as a novel approach to prevent isotretinoin-associated cheilitis. Dermatol Pract Concept. 2023;13(1):e2023012. DOI: https://doi.org/10.5826/dpc.1301a12

Accepted: September 22, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Isotretinoin (ISO)-associated cheilitis is the most common side effect and the most common reason for discontinuation of ongoing therapy. So, various lip balms are also routinely recommended for all patients.

Objectives: We aimed to investigate the effectiveness of local intradermal injections (mesotherapy) of dexpanthenol into the lips to prevent ISO-associated cheilitis.

Methods: This pilot study was conducted on patients over the age of 18 using ISO (about 0.5 mg/kg/day). All patients were prescribed only hamamelis virginiana distillate in ointment form as a lip balm. In the mesotherapy group (n=28), 0.1 ml of dexpanthenol was injected into each lip tubercle (4 points total) to the submucosal level. The patients in the control group (n=26) used only the ointment. “ISO cheilitis grading scale (ICGS)” was used in the evaluation of ISO-associated cheilitis. The patients were followed for 2 months.

Results: Although there was an increase in ICGS scores in the mesotherapy group compared to the baseline, no statistically significant change was observed after treatment (p=0.545). However, in the control group, there was a statistically significant increase in ICGS scores in the 1st and 2nd months compared to the baseline (p<0.001). Lip balms were needed significantly less frequently in the mesotherapy group compared to the control, both in the 1st and 2nd months (p=0.006, p=0.045; respectively).

Conclusions: Lip mesotherapy with dexpanthenol will be a useful option for preventing ISO-associated cheilitis because of its easy application, cost-effectiveness, low complication risk, and high patient satisfaction.
Introduction

Acne vulgaris is the most common disease in dermatology practice, which can occur at any age, especially in adolescents. Systemic isotretinoin (ISO, 13-cis-retinoic acid) is frequently prescribed for approximately 6-12 months in patients with moderate to severe acne vulgaris, based on a total cumulative dose of 120-150 mg/kg. [1,2] Despite its high efficacy, it has mucocutaneous side effects such as xerosis and cheilitis, which significantly affect the comfort of the patients’ life, as well as systemic side effects such as muscle-bone pain, headache, teratogenicity, lipid metabolism, and liver function impairment [1]. Side effects other than teratogenicity are thought to be dose-dependent [2]. Although long treatment duration and side effects are challenging for patients, it is a safe treatment [3]. Severe side effects may lead to dose reduction or termination of treatment. Therefore, it is crucial to control side effects in successful patient management.

ISO-associated cheilitis is the most common side effect caused by treatment-related reduction in sebum production, thinning of the stratum corneum, and changes in the skin barrier [2-4]. The frequency of cheilitis was found to be 77.5% at low doses (0.26-0.50 mg/kg/day) and 96.4% at high doses (0.76-1 mg/kg/day) [2]. It has been reported that the most common cause of patients’ ongoing-treatment refusal is cheilitis [2]. So, various lip balms/moisturizers are also routinely recommended for all patients prescribed ISO. The disadvantages of lip moisturizers are their cost, frequent use, and unsatisfactory results. Although vitamin E and omega-3 supplements have been reported to reduce ISO-associated mucocutaneous side effects, they have not been exactly adopted in practice yet [5,6].

Dexpanthenol (D-pantothenyl alcohol, provitamin B5) is frequently used as a topical and localized intradermal micro-injection (mesotherapy) in dermato-cosmetology and various diseases. Dexpanthenol moisturizes the skin thanks to its hygroscopic properties and repairs the skin barrier by hydrating the stratum corneum and reducing transepidermal water loss [7]. It has been commonly used as an over-the-counter topical drug for more than 70 years in diseases such as nappy rash, contact dermatitis, seborrhoeic dermatitis, cracked nipples, especially atopic dermatitis, and dry skin [7]. It supports skin regeneration and wound healing by increasing epidermal differentiation [8]. Also, it reduces inflammation after irritation with its anti-inflammatory properties [9,10]. Allergic reaction due to dexpanthenol is rare, and it is a safe agent [11]. Dexpanthenol may be useful in the prevention and treatment of ISO-associated cheilitis due to these properties.

Objectives

We aimed to investigate the effect of the combination of conventional topical lip balm and lip mesotherapy (dexpanthenol) in the prevention of ISO-associated cheilitis on patient satisfaction, need for moisturizer, and clinical outcomes.

Methods

This study was approved by the Local Ethics Committee (Decision No: 2021/12-186). The study was performed according to the latest version of the Helsinki Declaration and the Guidelines for Good Clinical Practice.

In the study protocol, the aim was not to investigate the superiority of mesotherapy over lip balm, but to evaluate the benefits of combining it with conventional topical care. This pilot study was conducted on patients who received ISO for the first time in Dermatology outpatient clinics between January 2021 and March 2021. Only patients over 18 years using about 0.5 mg/kg/day ISO were enrolled in the study. Written informed consent was obtained from all participants. Exclusion criteria from the study were the following: the presence of atopy, change of dose during follow-up, presence of any rheumatological disease, additional drug use, lip-licking/biting habit, acne excorie, immunodeficiency, local infection, using any steroid cream on the lips and dexpanthenol allergy.

In our practice, we recommend dexpanthenol mesotherapy to the lips in addition to lip balm to all eligible patients using ISO with a proactive approach to reduce the risk of cheilitis or dry lips. We have got quite positive feedback from this procedure, which has a low side effect profile. In this study, we retrospectively evaluated patients with and without dexpanthenol mesotherapy to the lips. We conventionally recommend a lip balm to every patient using ISO, even if lip mesotherapy has been applied. All patients included in the study were prescribed only hamamelis virginiana distil late in ointment form (Hametan® 25% ointment) as a lip balm. None of the patients used any additional product to moisturize their lips.

Firstly, 5% lidocaine pomade was applied to the lips of patients who approved the procedure. After waiting approximately 10-15 minutes, 0.1 ml of dexpanthenol (Bepanthen® 500 mg/2 ml Ampoule with the solution for injection) was injected into each lip tubercle (4 points in total) to the submucosal level (approximately 3-4 mm depth) using a 30 gauge-13 mm needle. During the follow-up with the patients, data such as the pain level of the procedure (Visual Analog Scale (VAS, 0-10 points)), possible side effects such as edema and ecchymosis, subjective satisfaction levels, and effect duration of the treatment were recorded. “ISO cheilitis grading scale (ICGS)” developed by Ornelas et al. was used in the evaluation of ISO-associated cheilitis [5] (Table 1).

All procedures were conducted using Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL, USA, v21.0). After checking the normality distribution of scale
variables by Shapiro Wilks, Wilcoxon and Friedman’s tests were used to compare two and more than two dependent groups, respectively. Bonferroni adjustment was applied as post-hoc (Wilcoxon signed-rank tests) after Friedman’s test (Bonferroni-adjusted two-sided significance level<0.05). Mann-Whitney U test was used for independent groups. Pearson’s chi-square test was used to compare independent categorical variables.

Results
The study involved 28 patients receiving dexpanthenol mesotherapy (mesotherapy group) and 26 patients without the procedure (control group, ointment only). The groups were identical in terms of age and sex distribution (p=0.917, p=0.627; respectively). The groups were identical for baseline ICGS (p=0.728). All patients were using ISO at a dose of approximately 0.5 mg/kg, and there was no statistical difference between the groups in terms of dosage (p=0.141) (Table 2).

The groups were compared with themselves and each other for the ICGS scores and frequencies of daily use of lip balm during the 2-month follow-up period (Table 3). In the mesotherapy group, despite the ISO treatment, although there was an increase in ICGS scores compared to the baseline, no statistically significant change was observed (p=0.545). However, there was a statistically significant increase in ICGS scores at the 1st and 2nd months of ISO treatment in the control group compared to the baseline (p<0.001). While there was no difference between the groups in terms of ICGS scores at baseline, there was a statistically significant difference at both 1 and 2 months (both, p<0.001) (Figure 1). The daily need for lip balm increased significantly in both groups compared to the baseline (both, p<0.001). However, in the mesotherapy group, lip balms were needed significantly less frequently compared to the control group both in the 1st and 2nd months of ISO treatment (p=0.006, p=0.045; respectively). As seen in Table 3, the patients had high satisfaction rates from dexpanthenol mesotherapy, and a statistically significant increase was observed after the 2nd session (p=0.005). According to 96.4% (n=27) of the patients, the effect of mesotherapy appeared in only 1-2 days. After two mesotherapy sessions, it was observed that the patients’ opinions about the effect duration of the treatment had altered. The effect duration was more than four weeks according to 26.1% of the patients, and 2-4 weeks according to 34.8%-65.2% of them. In the follow-up with the patients, mild angular cheilitis was observed in 3 (10.7%) patients in the mesotherapy group. The mean score of the procedure-related pain after topical anesthesia was 4.1±1.1. No additional complications were observed.

<table>
<thead>
<tr>
<th>Erythema</th>
<th>Scale/Crust</th>
<th>Fissure</th>
<th>Commissures</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No involvement</td>
<td>No involvement</td>
<td>No fissures</td>
</tr>
<tr>
<td>1</td>
<td>Mild erythema</td>
<td>Mild scale/crust</td>
<td>One fissure</td>
</tr>
<tr>
<td>2</td>
<td>Moderate erythema</td>
<td>Moderate scale/crust</td>
<td>Two to four fissures</td>
</tr>
<tr>
<td>3</td>
<td>Severe erythema</td>
<td>Severe scale/crust</td>
<td>Greater than four fissures</td>
</tr>
</tbody>
</table>

Total score: ranges from 0 to 12

Table 1. Isotretinoin Cheilitis Grading Scale.

<table>
<thead>
<tr>
<th></th>
<th>Mesotherapy group (n=28)</th>
<th>Control group (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>23.8 ± 3.2</td>
<td>24.0 ± 3.6</td>
<td>0.917</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>9 (32.1%)</td>
<td>10 (38.5%)</td>
<td>0.627*</td>
</tr>
<tr>
<td>Woman</td>
<td>19 (67.9%)</td>
<td>16 (61.5%)</td>
<td></td>
</tr>
<tr>
<td>Baseline ICGS</td>
<td>0.6 ± 0.7</td>
<td>0.6 ± 0.7</td>
<td>0.728</td>
</tr>
<tr>
<td>(ranging 0-12 points)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>22.3 ± 3.4</td>
<td>22.4 ± 2.9</td>
<td>0.890</td>
</tr>
<tr>
<td>Daily ISO-dose (mg/day)</td>
<td>29.6 ± 6.4</td>
<td>31.9 ± 4.0</td>
<td>0.142</td>
</tr>
<tr>
<td>Daily ISO-dose/kg (mg/kg/day)</td>
<td>0.50 ± 0.06</td>
<td>0.51 ± 0.05</td>
<td>0.141</td>
</tr>
</tbody>
</table>

ICGS: Isotretinoin Cheilitis Grading Scale, ISO: Isotretinoin
Mann Whitney U and Pearson’s chi-square* tests were used.
Table 3. Comparison of several parameters with dependent and independent groups.

<table>
<thead>
<tr>
<th>Grade score of ISO-associated cheilitis (ranging 0-12 points)</th>
<th>Baseline</th>
<th>1st month</th>
<th>2nd month</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesotherapy group (n=27)</td>
<td>0.6 ± 0.7</td>
<td>1.1 ± 1.3</td>
<td>0.8 ± 0.7</td>
<td>0.545</td>
</tr>
<tr>
<td>Control group (n=26)</td>
<td>0.6 ± 0.7</td>
<td>2.8 ± 0.7</td>
<td>3.4 ± 1.5</td>
<td>&lt;0.001&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>p-value **</td>
<td>0.728</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Frequency of daily use of lip balm (hamamelis ointment)

| Mesotherapy group (n=27)                                      | 0.9 ± 0.5 | 4.7 ± 2.3 | 4.3 ± 2.4 | <0.001<sup>a,b</sup> |
| Control group (n=26)                                          | 0.8 ± 0.7 | 6.0 ± 2.5 | 6.9 ± 4.6 | <0.001<sup>a,b</sup> |
| p-value **                                                     | 0.597     | 0.006     | 0.045     |           |

The patients’ opinions in the mesotherapy group regarding the treatment

| Satisfaction level (n=23)                                      | Very satisfied | 7 (30.4%) | 13 (56.5%) | 0.005     |
| Satisfied                                                     | -              | 14 (60.9%)| 10 (43.5%) |           |
| Slightly satisfied                                           | -              | 2 (8.7%)  | 0 (0.0%)   |           |
| Unsatisfied                                                   | -              | 0 (0.0%)  | 0 (0.0%)   |           |

Effect duration (n=23)

| ≥4 weeks                                                      | -              | 6 (26.1%) | 6 (26.1%) | 0.106     |
| 2-4 weeks                                                    | -              | 8 (34.8%) | 15 (65.2%)|           |
| ≤2 weeks                                                     | -              | 9 (39.1%) | 2 (8.7%)  |           |

Data are expressed as mean ± standard deviation.

* Wilcoxon and Friedman’s tests were used for comparisons of two and more than two dependent groups, respectively. Bonferroni adjustment was applied as post-hoc (Wilcoxon signed-rank tests) after Friedman’s test (Bonferroni-adjusted significance level<0.05).
** Mann Whitney U test was used for independent groups.

a: p<0.05 for the difference between baseline and 1<sup>st</sup> month; b: p<0.05 for the difference between baseline and 2<sup>nd</sup> month; c: p<0.05 for the difference between 1<sup>st</sup> month and 2<sup>nd</sup> month in 2-month patient follow-up.

Figure 1. ISO-associated mucositis was significantly lower in the mesotherapy group than in the control group both at 1<sup>st</sup> month and 2<sup>nd</sup> months when compared by ICGS scores.
ICGS: Isotretinoin cheilitis grading scale, CI: Confidence interval.
Conclusions

Cheilitis is characterized by erythema, dryness, crusting, fissures, and inflammation of the commissures on the lips. It greatly affects the quality of life of patients due to burning, itching, and edema [5]. Various sub-clinical types of cheilitis can be encountered secondary to different etiological factors such as actinic damage, systemic diseases, immunosuppression, nutritional deficiencies, local irritants and allergens, infections, and drugs [9,10]. The main cause of drug-associated cheilitis is systemic retinoids [10]. ISO is an indispensable and safe agent of dermatology practice with high cure rates for acne vulgaris [1]. However, it should not be overlooked that ISO-associated cheilitis is the leading cause of early termination of treatment, with a rate of 1.4% [2]. Effectively reducing the risk of cheilitis will increase patient comfort and treatment sustainability. Although various supplements such as vitamin E, omega 3, and primrose oil have been recommended in some studies for mucocutaneous side effects, there is no established treatment method other than moisturizers [6,11,12]. In randomized controlled studies, it was reported that vitamin E supplementation did not significantly reduce the xerosis associated with ISO [13,14]. Patients may not be willing to use another systemic therapy while also undergoing long-term ISO therapy. Therefore, we consider it to be challenging to use oral supplements in practice. We introduce lip mesotherapy with dexpanthenol as a novel approach.

We have experienced highly satisfactory results with lip mesotherapy with dexpanthenol, which has a high safety profile and which we frequently prefer in indications such as hair loss, wound healing, and rejuvenation. To the best of our knowledge, the effectiveness of dexpanthenol in lip mesotherapy has not been reported so far. In this study, we found that dexpanthenol mesotherapy combined with topical therapy has excellent efficacy in preventing ISO-associated cheilitis. While there was no difference between the groups in terms of the severity of baseline cheilitis and the frequency of lip balm use before treatment, both parameters were lower in the mesotherapy group compared to the control group in both 1st and 2nd-month examinations. However, even if mesotherapy is performed in patients using ISO, topical care should be offered to every patient due to the significant increase in the need to use lip balm. The clinical results recorded in the follow-up of the patients in the mesotherapy and control groups after ISO were presented in Figure 2 and Figure 3, respectively.

It is assumed that mesotherapy allows slower diffusion, higher levels, and longer-lasting effects of drugs in the tissues around the injection site compared to intramuscular injection or topical applications [15]. This method is a safe transdermal drug delivery tool applied by injecting vitamins, minerals, and various bioactive substances into the skin layers to stimulate fibroblast activity and collagen genesis and reverse elastin degeneration and transepidermal water loss [15,16]. Patients may experience injection-related side effects such as pain, erythema, edema, and ecchymosis. Only one of the patients in the study hesitated to continue treatment because of pain. The patients stated that they had no experience of any bruising or ongoing pain after the procedure and that the edema on the lips usually regressed within 1-2 hours. Mild-moderate pain was noted despite topical anesthesia. We think that this may be reduced further by adding lidocaine solution to dexpanthenol. Since we observed angular cheilitis in some patients, although the vermilion was normal, we concluded that 0.05-0.1 ml dexpanthenol mesotherapy to the lip commissures, in addition to 4-point injection, would yield better clinical results. The satisfaction rates of the patients were high, and the significant increase
and gene regulation effects of dexpanthenol on dermal fibroblasts [8,19,20]. We think dexpanthenol injected into the submucosa reduces the severity of cheilitis and the need for moisturizer by increasing hydration and regeneration in ISO-damaged skin, reducing irritation. There are limited studies comparing the efficacy of mesotherapy compared to topical applications of the same agent. While there is no research on the efficacy of dexpanthenol, submucosal injection of vitamin C in gingival hyperpigmentation has been found to be superior to the use of its topical form [21].

Although the main limitation is a small sample size, statistically significant high efficacy rates were achieved. Transepidermal water loss measurement was not included in the protocol due to technical impossibility. The shortcoming of the study was that we could not compare dexpanthenol mesotherapy with the topical form of dexpanthenol and placebo. The non-reimbursement of dexpanthenol ointment and the excessive diversity of similar products on the market necessitated the use of hamamelis virginiana as a control group in our retrospective study. Because hamamelis virginiana (Hametan® ointment), an alternative to dexpanthenol, is one of the most frequently preferred reimbursed medical products in our country. Indeed, Wolff and Kieser investigated the clinical effects of ointment forms of hamamelis and dexpanthenol in the treatment of skin/mucous membrane inflammation in children [22]. Accordingly, physicians’ and parents’ efficacy assessments revealed similar or better treatment ratings of hamamelis ointment than dexpanthenol. While it is plausible that water intake reduces the mucocutaneous side effects of ISO, there is no evidence to our knowledge. Therefore, water intake is lacking in the study protocol.

In conclusion, the effectiveness of lip mesotherapy with dexpanthenol in the prevention of ISO-associated cheilitis was remarkable. We believe that this method will be a useful adjuvant option for both the prevention and treatment of ISO-associated cheilitis because of its easy application, low cost, low complication risk, and high patient satisfaction. However, patients’ opinions and approvals on whether they want such a needle application should be evaluated. Further placebo-controlled, randomized studies with larger sample sizes are needed.

References

3. Brito ME, Sant’Anna I, Galindo J, Rosendo I, Santos J. Evaluation of clinical adverse effects and laboratory alterations in the satisfaction rates after the second session was remarkable. It has been claimed that the most disturbing period in ISO-associated cheilitis is the first month of treatment, after which patients adapt to xerotic changes [11]. The increase in the satisfaction levels of the patients after the second session may be related to this adaptation process.

Dexpanthenol is an important molecule for the physiological function of the epithelium. After absorption through the skin, it quickly turns into pantothenic acid, a component of coenzyme-A. Coenzyme-A is an essential cofactor in the metabolism of carbohydrates, fatty acids, sphingolipids, proteins, sterols, and steroid hormones [12]. Dexpanthenol interacts with the relevant lipid and protein molecular segments in the corneocytes, thus increasing the hydration of the skin by contributing to molecular fluidity [17,18]. Studies have demonstrated the migration, proliferation,
The Effect of Covid-19 on the Hair Diseases Observed in Health Care Providers: Analysis of 513 Participants

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Key words: Covid-19, hair diseases, surveys, questionnaires

Citation: Bostan E, Cakir A. The Effect of Covid-19 on the Hair Diseases Observed in Health Care Providers: Analysis of 513 participants. Dermatol Pract Concept. 2023;13(1):e2023036. DOI: https://doi.org/10.5826/dpc.1301a36

Accepted: June 17, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The Covid-19 pandemic has been shown to have major acute and chronic impacts on the skin. Various studies reported that there has been an increase in the number of patients referred to outpatient dermatology clinics with the complaint of variable hair diseases during the era of Covid-19. Hair seems to be substantially affected by both the infection itself and anxiety/stress provoked by the pandemic. Therefore, understanding the impact of Covid-19 on the clinical course of variable hair diseases has become a major concern in dermatology practice.

Objectives: To examine the frequency and types of various hair diseases, both new-onset and ingravescent, observed in healthcare providers.

Methods: A web-based questionnaire related to the hair diseases seen in healthcare providers both prior to the Covid-19 pandemic and after the start of the pandemic was created. The type of both new-onset and pre-existing hair diseases and ongoing hair diseases observed during Covid-19 were investigated.

Results: A total number of 513 participants were included in the study. One hundred seventy cases were diagnosed with Covid-19. During the Covid-19 pandemic, 228 reported having at least one hair disease; the most common one being telogen effluvium, followed by hair greying and seborrheic dermatitis. There was a statistically significant relationship between the presence of a new-onset hair disease during the pandemic and being diagnosed with Covid-19 (p=0.004).

Conclusion: Our study shows that Covid-19 infection has a significant impact on the emergence of new-onset hair diseases.
Introduction

The Covid-19 pandemic has been shown to have a negative influence on both skin diseases and the dermatological life quality of healthcare providers (HCPs) [1]. Skin serves as one of the first-line-of-defense components of the body against numerous pathogens by forming a physical barrier [2]. Continuous use of personal hygiene equipment impairs the skin barrier, causing skin problems such as drying, lichenification and itching further aggravating a previously-existing dermatological disease or resulting in the development of a new-onset skin disorder [1].

Hair is a skin appendage whose cycle is frequently affected by various external factors including nutritional deficiencies, endocrinopathies, major surgical operations and systemic diseases [3]. In a normal hair cycle, approximately 90% of the hairs are in the anagen phase [4]. The catagen phase begins when the anagen phase ends and approximately 5% of all hair shafts are in the catagen phase at any given time [4]. In the anagen phase, hair follicles continue to grow whereas in the catagen phase, hair follicles start to dwindle and hair growth stops [5]. The telogen phase or ‘resting phase’ lasts about three months and 10-15% of all hairs are in the telogen phase in a normal hair cycle [4,5]. Following the telogen phase, hair shafts fall out. Telogen effluvium (TE) presents itself in the form of excessive hair shedding resulting from the rapid entry of anagen hairs into the telogen phase [3].

The normal cycle of hair growth is influenced and disrupted by various internal and external factors including severe systemic infections such as Covid-19 [6]. Covid-19-induced mild and severe TE cases have continued to be reported in increasing numbers from the start of the pandemic [6,7]. Alopecia areata (AA), an autoimmune hair disorder; seborrheic dermatitis (SD), a chronic inflammatory skin disease; trichotillomania, a psychodermatologic hair disorder are some other entities that are increasingly observed in the era of Covid-19 [8-10]. Both adverse psycho-social effects of the pandemic and cytokine storm induced in the setting of Covid-19 infection are implicated in the development of these hair diseases [6].

In our study, we aimed to investigate the frequencies and types of both new-onset and pre-existing variable hair diseases observed in HCPs during the Covid-19 pandemic.

Methods

Local ethics committee approval was obtained for the present study (the date and decision number: November 19 2021, 2021/028). A web-based survey consisting of 22 questions (Supplementary file 1) was created using Google forms. The survey included four sections: (I) personal information; (II) Covid-19 infection; (III) hair diseases seen prior to the onset of the Covid-19 pandemic; (IV) hair diseases observed during the Covid-19 pandemic. The online questionnaire was carried out among HCPs and a virtual snowball sampling method was used.

IBM SPSS for Windows Version 20.0 was used for the statistical analysis. For descriptive analysis, numerical variables were given as mean ± standard deviation (range: minimum-maximum) and categorical variables were shown as percentages and frequencies. Chi-Square test was used to analyze the relationships between the categorical variables. P values of <0.05 were considered statistically significant.

Results

A total number of 513 HCPs were included in the study. The mean age was 34.84 ± 8.90 years (minimum:19, maximum:66). Three hundred fifty-eight (69.8%) of the respondents were female whereas 155 (30.2%) were male. Two hundred forty-one (47%) respondents reported having Covid-19 related symptoms; whereas 272 (53 %) didn’t exhibit any symptoms. Three hundred twenty-nine (63.2%) participants had a history of close contact with someone with a confirmed diagnosis of Covid-19. Covid-19 real-time polymerase chain reaction test (RT-PCR) was performed on 445 (86.7 %) respondents; 156 (35.1%) cases tested positive, whereas 289 (64.9%) tested negative. Additionally, 14 cases who did not give RT-PCR test or tested negative, were diagnosed with Covid-19 via radiological imaging. So, a total of 170 cases were accepted to have a confirmed diagnosis of Covid-19. Only 12 patients were required to be hospitalized for severe Covid-19 infection.

During the online questionnaire, participants were asked if they had any other contributing factors during the Covid-19 pandemic that might have played a role in the development or worsening of their hair diseases. Thirty-six (7%) cases had a pregnancy, one (0.2%) respondent was receiving chemotherapy, 21 (4.1%) were dieting, 12 (2.3%) had a major surgical operation, 20 (3.9%) had intentional/unintentional loss of more than 5% of their own weight in a period of 6 months during the Covid-19 pandemic. Lastly, 162 (31.6%) participants reported feeling stressed, which had a major impact on their lives during the Covid-19 pandemic. Two hundred fifty-four (49.5%) respondents had at least one hair disease prior to the start of the Covid-19 pandemic. The frequencies and percentages of different types of hair diseases observed in the pre-Covid-19 era are shown in Table 1.

Of 513 patients, only 40 patients had new-onset hair disease that developed during the Covid-19 pandemic. Out of 40 patients, 25 (62.5%) had new-onset TE, 12 (30%) reported increased hair greying, 6 (15%) had new-onset...
female-pattern hair loss (FPHL), 3 (7.5%) had new-onset male-pattern hair loss (MPHL), 4 (10%) reported trichodynia, 2 (5%) reported new-onset SD, 2 (5%) reported new-onset trichotillomania and 1 (2.5%) reported new-onset scalp psoriasis. Of these 40 patients, only 20 (50%) were diagnosed with Covid-19. The mean duration between the emergence of the new-onset hair disease and Covid-19 diagnosis was 1.24 ± 0.83 months (minimum: 0.25, maximum:3). Of 25 patients with new-onset TE during the Covid-19 pandemic, 22 (88%) had been tested for SARS-CoV-2 infection. Fourteen (63.6%) out of 22 patients had a positive RT-PCR result. For these patients, the mean time interval between the diagnosis of Covid-19 and the approximate commencement of the acute TE was 1.13 ± 0.66 months (minimum: 0.3, maximum:3). During the era of Covid-19, 228 (44.4%) reported having any hair disease (including pre-existing, ongoing and new-onset ones); the frequencies and percentages of different types of hair diseases observed in the Covid-19 era are shown in Table 1. Of 228 individuals with a history of any hair disease during Covid-19, 34 (14.9%) had been diagnosed by a physician. Participants who had the same hair disease prior to the Covid-19 pandemic and during the Covid-19 pandemic were asked to express their opinion about the course of the hair disease during the Covid-19 pandemic. Out of 259 respondents, 129 (49.8%) indicated that there was no change, 121 (46.7%) reported an increase in the sign and symptoms of the specified hair disease whereas 9 (3.5%) claimed that the severity of the hair disease decreased. Of 121 patients who reported an increase in the severity of the pre-existing hair disease during the Covid-19 pandemic, 51 (42.1%) had TE, 37 (30.6%) had hair greying, 29 (24%) were diagnosed with SD, 16 (13.2%) had symptoms of trichodynia, 16 (13.2%) had FPHL, 12 (9.9%) were diagnosed with MPHL, 7 (5.8%) had trichotillomania, 5 (4.1%) were suffering from scalp psoriasis, 2 (1.7%) had AA and only 1 (0.8%) patient had alopecia totalis. Again, of 121 individuals who reported an increase in the severity of the hair disease and 40 who had new-onset hair disease during the Covid-19 pandemic, 138 (85.7%) thought that stress and anxiety played a role either in the development of the new-onset hair disease or deterioration of the pre-existing disease.

A statistically significant relationship was found between Covid-19 RT-PCR positivity and the presence of any hair disease during the Covid-19 pandemic (p=0.009) (Table 2). In addition, a statistically significant relationship was present between Covid-19 RT-PCR positivity and the presence of any new-onset hair disease during the Covid-19 pandemic (p=0.002). The distribution of Covid-19 RT-PCR results in relation to the presence of any new-onset hair disease during the Covid-19 pandemic is shown in Figure 1. The distribution of Covid-19 infection status in relation to the presence of any hair disease during the Covid-19 pandemic is shown

Table 1. Frequencies and percentages of different types of hair diseases in the pre-Covid-19 and Covid-19 pandemic eras.

<table>
<thead>
<tr>
<th>Type of Hair Disease</th>
<th>Pre-Covid-19 (n, %)</th>
<th>Covid-19 (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male pattern hair loss</td>
<td>36 (13.9)</td>
<td>29 (12.7)</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>13 (5)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Female pattern hair loss</td>
<td>30 (11.6)</td>
<td>33 (14.5)</td>
</tr>
<tr>
<td>Alopecia totalis</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Telogen effluvium</td>
<td>108 (41.7)</td>
<td>111 (48.7)</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>63 (24.3)</td>
<td>52 (22.8)</td>
</tr>
<tr>
<td>Scalp psoriasis</td>
<td>9 (3.5)</td>
<td>9 (3.9)</td>
</tr>
<tr>
<td>Trichodynia</td>
<td>35 (13.5)</td>
<td>32 (14)</td>
</tr>
<tr>
<td>Trichotillomania</td>
<td>18 (6.9)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Increased hair greying</td>
<td>72 (27.8)</td>
<td>71 (31.1)</td>
</tr>
<tr>
<td>Total</td>
<td>259 (100)</td>
<td>228 (100)</td>
</tr>
</tbody>
</table>

Table 2. Statistically significant relationship was found between the Covid-19 RT-PCR positivity and having at least one hair disease during the Covid-19 pandemic (p=0.009).

<table>
<thead>
<tr>
<th>Covid-19 RT-PCR Results</th>
<th>Presence of any hair disease during Covid-19 pandemic</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not present n (%)</td>
<td>Present n (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>169 (70.4)</td>
<td>120 (58.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>71 (29.6)</td>
<td>85 (41.5)</td>
</tr>
<tr>
<td>Total</td>
<td>240 (100)</td>
<td>205 (100)</td>
</tr>
</tbody>
</table>
difference between developing new-onset hair disease and having at least one contributing factor that may be related to the pathogenesis of the new-onset hair disorder (p=0.119).

Discussion

From the start of the Covid-19 pandemic, numerous cutaneous manifestations of the infection itself along with the occupational skin problems which result from the continuous use of personal protective equipment have been reported in the literature [11,12]. Urticaria, maculopapular eruption, angioedema, vesicular eruption, pityriasis rosea, erythema
A relationship with hair cortisol concentration as a biomarker of stress was sought. In a study population of 234 HCPs, 40% showed hair cortisol concentration outside of the normal range [16]. In this study, positive correlation between hair cortisol concentration versus perceived stress and direct correlation between hair cortisol concentration versus emotional exhaustion were also found [16]. This study again underlies the fact that HCPs are exposed to emotional stress and burnout syndrome during the pandemic and hair is largely influenced by the psychosocial impacts of Covid-19. In correlation with this research, in our study of 161 participants who either reported an increase in the severity of the pre-existing hair disease or had new-onset hair disease during the Covid-19 pandemic, 138 (85.7%) thought that stress and anxiety contributed to the development of the new-onset hair disease or progression of the pre-existing disease.

Cases of TE and trichodynia have been observed to increase in number from the start of the pandemic [6,17]. Rizzetto et al [6] reported three cases of TE observed after severe SARS-CoV-2 infection. Furthermore, Mieczkowska et al [18] described a case series consisting of 10 women who were diagnosed with Covid-19 via RT-PCR and antibody test. These patients didn’t have any other triggering factor that would induce TE and TE started 3 to 7 months after Covid-19 infection. In another retrospective study by Cline et al [19], it is found that there was a >400% increase in the number of patients diagnosed with TE between July and August 2020 when compared to the number of patients diagnosed with TE between November 2019 and February 2020. In another multi-centered study, 214 patients who were diagnosed with acute TE after SARS-CoV-2 infection were

Table 3. The distribution of Covid-19 infection status in relation to the presence of any new-onset hair disease during the Covid-19 pandemic.

<table>
<thead>
<tr>
<th>Diagnosed with Covid-19 by RT-PCR testing or radiological imaging</th>
<th>Presence of any new-onset hair disease during Covid-19 pandemic</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not present n (%)</td>
<td>Present n (%)</td>
</tr>
<tr>
<td>No</td>
<td>156 (72.9)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Yes</td>
<td>58 (27.1)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>214 (100)</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>

Table 4. The distribution of having a new-onset hair disease with regard to the presence of one or more contributing factors for hair disease development.

<table>
<thead>
<tr>
<th>Presence of any new-onset hair disease during Covid-19 pandemic</th>
<th>Presence of at least one precipitating factor linked to hair disease</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not present n (%)</td>
<td>Present n (%)</td>
</tr>
<tr>
<td>Not present</td>
<td>145 (86.8)</td>
<td>69 (79.3)</td>
</tr>
<tr>
<td>Present</td>
<td>22 (13.2)</td>
<td>18 (20.7)</td>
</tr>
<tr>
<td>Total</td>
<td>167 (100)</td>
<td>87 (100)</td>
</tr>
</tbody>
</table>
evaluated [20]. The mean age was 47.4 years and 78.5% of all patients were female, 86.4% developed a fever during the infection. Additionally, 20.8% of patients required hospitalization and the mean time interval between the Covid-19 diagnosis and significant hair shedding was 57.1 days [20]. In our study cohort, only 40 patients developed new-onset hair disease during the Covid-19 pandemic and the most frequently observed new-onset hair disease was TE. Of these 25 patients with TE, 22 were tested for SARS-CoV-2 infection. Fourteen out of 22 patients had been diagnosed with Covid-19. In our research, the mean time interval between the diagnosis of Covid-19 and the start of hair shedding was found to be 1.13 ± 0.66 months.

Trichodynia is defined as a painful sensation in the scalp often accompanied by TE [21]. Di Landro et al [17] observed 39 patients who presented with TE after Covid-19 infection. Of 39 patients, 7 patients also suffered from severe trichodynia. In this study, the mean age was 64.6 years and both the excessive hair shedding and trichodynia resolved within 2 to 4 months. The authors argued that the hyperinflammatory environment developing in the setting of SARS-CoV-2 infection, was the most probable cause of TE and trichodynia since interleukin-6, interleukin-18 and tumor necrosis factor-α were shown to induce transition to the catagen phase in hair follicles [17,22]. In our research, 4 new-onset trichodynia cases were detected whereas 16 participants reported exacerbation in trichodynia symptoms during the Covid-19 pandemic.

MPHL is a common hair disease which is characterized by patterned, progressive thinning of hair, seen in genetically susceptible men. The presence of MPHL is thought to be correlated with severe Covid-19 infection [23]. The priming of SARS-CoV-2’s spike protein requires transmembrane protease, serine 2 (TMPRSS2) activity [23]. TMPRSS2 gene transcription is dependent upon androgen receptor activity, so it seems plausible that men are more vulnerable to SARS-CoV-2 infection and fatality rates are rare before puberty [23]. Lee et al [24] evaluated 1605 patients who tested negative for Covid-19 and 336 patients who were diagnosed with Covid-19. The two groups didn’t have any difference in terms of mean age and body mass index [24]. In this study, it was shown that Covid-19 positivity correlated with the increasing baldness score (determined by the Hamilton-Norwood scale) [24]. In another study, 41 Caucasian males who were hospitalized with a diagnosis of SARS-CoV-2 pneumonia were evaluated [25]. Twenty-nine (71%) had clinically evident androgenetic alopecia (Hamilton-Norwood scale > 2) and 12 (29%) patients had a Hamilton Norwood scale of 1 or 2 [25]. In another study by Muller Ramos et al [26], it was proven that alopecia and grey hair are correlated with Covid-19 severity. In our study, of 170 patients diagnosed with Covid-19, 21.8% reported having MPHL and/or increased grey hair prior to the pandemic. Out of 37 patients, only 5 required hospitalization for Covid-19.

AA is an autoimmune, inflammatory, non-cicatricial alopecia which is characterized by relapsing and recurring episodes of patchy or diffuse hair loss. In the hyperinflammatory state of Covid-19, plasma levels of tumor necrosis factor-α, interferon-γ, interleukin-2 and interleukin-1β which are also involved in the pathogenesis of AA, rise substantially [27]. In a study by Rudnicka et al [28], 32 patients with mild-to-moderate AA were evaluated 1-6 weeks before Covid-19 infection and 3 months after the infection [28]. It was found that Covid-19 infection didn’t have any negative impact on the clinical course of AA [28]. In another study with 392 AA patients, 42.5% had disease relapse about 2 months after Covid-19 infection whereas disease relapse was observed in 12.5% of all participants without a confirmed diagnosis of SARS-CoV-2 infection [29]. In our study, no new-onset AA was identified, but only 2 (15.4%) out of 13 patients with a pre-existing diagnosis of AA reported an increase in the severity of symptoms.

SD is a chronic inflammatory skin disorder characterized by erythema, greasy scaling and itching which most commonly occurs in the scalp, eyebrows, ears and face [30]. A study by Veraldi et al [30], showed that disease severity increased in 46.5% of the patients diagnosed with SD. These patients reported wearing anti-Covid-19 masks for 6 to 10 hours a day and 35% of the patients with worsening SD were health workers [30]. It was asserted that the high temperature and humidity induced by the use of face masks cause abnormalities in microbiota and enhance sweating, thereby provoking an irritant reaction and itching [30]. In line with the results of this study, 29 (90.6%) out of 32 participants with a previous diagnosis of SD, reported an increase in the severity of symptoms of the disease during the pandemic. The higher percentage of participants in our study is not surprising since we have included only HCPs in our study.

Trichotillomania is characterized by repetitive urges to pull out hair from the scalp, eyebrows or other parts of the body [31]. Low self-confidence, social anxiety, major depression and psychosocial dysfunction are associated with trichotillomania [31]. In a study by Pathoulas et al [32], 460 patients presented with a self-reported diagnosis of body-focused repetitive behaviors, 181 patients had a hair-pulling disorder, whereas 141 reported both hair-pulling and skin-picking disorders. A majority of the patients reported an increase in their symptoms during Covid-19 [32]. Our results showed that 38.9% of the individuals with a diagnosis of trichotillomania prior to the pandemic reported having incremental symptoms during Covid-19.

In conclusion, if we were to look at the results of our study altogether, we want to highlight that a statistically significant relationship exists between being diagnosed with
Covid-19 and having at least one specific hair disease during the Covid-19 pandemic. Additionally, there seems to be a statistically significant relationship between having a new-onset hair disease during the pandemic and being diagnosed with Covid-19. Our study indicates that hair is vulnerable to the direct effects of SARS-CoV-2 infection and indirect effects of the pandemic (psychosocial impacts, skin problems resulting from the use of personal protective equipment etc.). We believe that the underlying etiopathological mechanisms of the trichological effects of Covid-19 are also possibly related to other pre-existing, ongoing and new-onset (post-Covid-19) systemic as well as dermatological manifestations.

Our research has some limitations since not all the participants were diagnosed by a dermatologist. The severity of the hair disease was not directly evaluated by a physician using a score or scale, so the results might have been subjective. Prospective, randomized-controlled studies with larger sample sizes are needed to confirm our results.

References


Lead Time from First Suspicion of Malignant Melanoma in Primary Care to Diagnostic Excision: a Cohort Study Comparing Teledermatoscopy and Traditional Referral to a Dermatology Clinic at a Tertiary Hospital

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Key words: teledermatoscopy, dermatoscopy, lead time, malignant melanoma, general practitioner

Citation: Schultz K, Ivert LU, Lapins J, Sartorius K, Johansson EK. Lead Time From First Suspicion Of Malignant Melanoma In Primary Care To Diagnostic Excision: A Cohort Study Comparing Teledermatoscopy And Traditional Referral To A Dermatology Clinic At A Tertiary Hospital. Dermatol Pract Concept. 2023;13(1):e2023018. DOI: https://doi.org/10.5826/dpc.1301a18

Accepted: June 8, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The increasing use of teledermatoscopy in clinical practice has led to demands to evaluate the effects of this new technology on traditional healthcare systems.

Objectives: To study lead times from first consultation in primary care to diagnostic excision of suspected malignant melanoma lesions in traditional referrals to a tertiary hospital-based dermatology clinic compared with mobile teledermatoscopy referrals.

Methods: A retrospective cohort study design was used. Data on sex, age, pathology, caregivers, clinical diagnosis, date for first visit to primary care unit, and date for diagnostic excision were collected from medical records. Patients managed through traditional referral (n=53) were compared with patients managed at primary care units using teledermatoscopy (n=128) regarding lead time from first visit to diagnostic excision.
Introduction

Sweden has one of the highest incidence rates of cutaneous melanoma in Europe and the incidence is increasing, as in most areas with fair-skinned populations, e.g., North America, northern Europe, Australia, and New Zealand [1]. Diagnosing malignant melanoma at an early stage remains the most important predictor of melanoma survival [2]. Most patients have their first consultation in primary care (PC) and improved management of suspicious pigmented lesions in this setting is needed. Increasing digitalization in healthcare, including teledermatoscopy (TDS), could be a promising instrument for skin cancer care [3-5].

It is well-established that dermatoscopy, in experienced hands, increases diagnostic accuracy for both melanocytic and non-melanocytic lesions [6-13]. Finnane et al. found in their review that teledermatology consistently reduced waiting times for assessment and diagnosis, with high patient satisfaction [14], and studies indicate that lead times for patients with suspected malignant melanoma can be reduced if TDS is used for triage [15-18]. Moreover, double reading of images has been shown to improve diagnostic performance in telemedicine settings [19-21]. The evolution of smartphone-attached dermatoscopes and smartphone applications makes TDS increasingly convenient to use [22,23]. The role of TDS in managing skin cancer, including the lead time from the first visit in PC to diagnostic excision, needs further exploration [4,14].

The region of Stockholm, Sweden, has 2.4 million inhabitants, with access to more than 200 primary care units (PCUs). Patients with suspected skin cancer usually visit a PCU, are evaluated by PC physicians, and, if needed, referred to a dermatologist at either an out-of-hospital or a hospital-based dermatology clinic.

In 2015, in Sweden, a guideline on urgent cancer referral pathways (standardized care (SC) pathways) was implemented for cancer care, including malignant melanoma care [24]. In cases reasonably suspicious of malignant melanoma, a fast-track SC pathway starts and the PC physician labels the referral “SC pathway cutaneous melanoma.” The SC pathway’s ideal time frame from reasonable suspicion of melanoma to initiation of treatment (diagnostic excision) is seven days.

In 2015, a mobile TDS pilot project was initiated and funded by the Stockholm health authorities at the Regional Cancer Center. In the final implementation of the project, the intention is to include all 200 PCUs in the Stockholm region by 2023.

Objectives

The aim of this study was to investigate potential differences in lead time from suspicion of malignant melanoma to excision when using TDS in PC compared with traditional referral (TR) to a tertiary dermatology center.

Methods

Setting

For the present TDS project, PCUs use a dedicated mobile platform (Dermicus, Gnosco AB, Sweden). From 2015, PCUs in the Stockholm region were recruited. They could participate cost-free. The equipment (dermatoscope and phone) was free for PCs. In 2019 there were two to four physicians active per PCU, with a total of 230 cases per month. PC physicians received an introduction to the equipment and a brief online dermatoscopy course. They chose which lesions and the number of lesions to refer without the involvement of a dermatologist. In the clinic, PC physicians take photos of suspected lesions with a smartphone (iPhone 6S, Apple Inc.), attached to a dermatoscope (Heine ic1; Heine Optotechnik, Herrsching, Germany). An overview, a close-up, and two dermatoscopic images (polarized, unpolarized) are collected and uploaded to a database (Fig. 1,2). The images and background information (e.g., patient age and sex, history of changes and symptoms) are reviewed and dermatoscopic images analyzed through double reading. A consultation report is issued by at least two dermatologists in consensus. The dermatologists are trained in dermatoscopic diagnosis of

Results: Mean time from date of first visit at primary care unit to diagnostic excision did not differ between the traditional referral and teledermatoscopy groups (16.2 vs. 15.7 days, median 10 vs. 13 days, p=0.657). Lead times from date of referral to diagnostic excision did not significantly differ (15.7 vs. 12.8 days, median 10 vs. 9 days, p=0.464).

Conclusions: Our study indicates that lead time to diagnostic excision for patients with suspected malignant melanoma managed by teledermatoscopy was comparable and not inferior to that of the traditional referral pathway. If teledermoscopy is used at first consultation in primary care, it could potentially be more efficient than traditional referral.
Figure 1. Process of mobile teledermatoscopy as used in the project. The primary care physician examines the patient, takes clinical and dermatoscopic images (A and B), and fills in clinical information which is then packaged together in the mobile app and sent encrypted to a database. Photo by Oscar Segerström, Medicinsk bild, Karolinska Hospital.

Figure 2. Photographs of a teledermatoscopy case. (A) An overview, (B) a close-up, and two dermatoscopic images ((C) polarized, (D) unpolarized) are collected and uploaded in the mobile application together with background information. Histopathologic diagnosis: Lentigious malignant melanoma in situ described in pathology report as an extensive atypical junction melanocytic proliferation, lentigious and nested, with frequent rete fusion, multifocal pagetoid upgrowth and early involvement of adnexal structures. The lesion focally blends with areas of seborrheic keratosis-like epidermal reaction and a small benign intradermal nevus is noted at the periphery of the main lesion.
cutaneous malignancies. The PC physician is provided with a dermatoscopic description of the lesion with a preferential diagnosis and a recommendation for management (Fig. 3). If the lesion is unequivocally benign, no action beyond information to the patient is recommended. In equivocal flat lesions, a short-term digital dermatoscopic follow-up or excision may be recommended. If melanoma is suspected, the recommendation is an urgent excisional biopsy starting the SC pathway. The diagnostic excision is performed at the PC clinic or, if necessary, referred to a specialist.

Study Design and Study Population
All patients managed on the SC pathway due to suspected malignant melanoma 1) at a tertiary dermatology clinic, Södersjukhuset or 2) in the TDS project were recruited to this cohort study. Data were collected from electronic medical records. Patients aged 18 years and older were included. Referrals for specific suspected melanoma lesions that were considered high-priority were selected. Data on sex, age, pathology, caregivers, clinical diagnosis, date of first PCU visit, and date of diagnostic excision, were collected.

Traditional Referral (TR) Group
During the study period from 1 January 2016 to 19 December 2018, 274 patients that were referred to the hospital-based dermatology unit at Södersjukhuset (tertiary DU) and labelled as having suspected melanomas on the SC pathway were identified. Of those 274 referrals, 66 from 29 different PCUs met the inclusion criteria: the purpose of the referral was a specific suspected melanoma that was considered high-priority by the hospital consultant and planned for an in-person visit within two weeks. All referrals in the study were sent in electronic format and prioritized by the dermatologist at tertiary DU on the same date as referrals from PCU were sent.

Teledermatoscopy (TDS) Group
In the period between 1 January 2016 and 26 March 2019, 52 PCUs generated 3,850 individual referrals for TDS. When searching for lesions labelled as suspected melanoma during this period, a total of 200 patients were identified. Fifty-five lesions were excluded based on not being labelled as cases for the SC pathway, 12 had no available electronic medical records, and one was evaluated by only one dermatologist. In all, 132 referrals met the criteria in the TDS group: at least two dermatologists in consensus stated that the suspicion of malignant melanoma was high and that the SC pathway for melanoma was recommended.

Primary Outcome
Lead time (days) from the date of first PCU visit to the date of diagnostic excision.

Secondary Outcome
Lead time (days) from date of referral to tertiary DU or TDS to date of diagnostic excision.

Figure 3. Example of a teledermatoscopy case. The primary care physician fills in clinical information. Two dermatologists assess the case independently and provide a detailed description of the dermatoscopic findings, a provisional diagnosis, and a consensus recommendation for further diagnostic action.
Results

A total of 198 patients (one unique lesion per patient) were included in the study, 66 in the TR group and 132 in the TDS group (Fig. 4). The background characteristics and a summary of diagnoses are shown in Tables 1 and 2, respectively. No significant differences were observed in age, sex, lesion diameter, or the proportion of histopathologically confirmed melanomas. The proportion of invasive melanoma was significantly larger in the TR group than in the TDS group (p=0.028) and invasive melanomas were significantly thicker in the TR group (p=0.005). The proportion of melanoma in situ was larger in the TDS group (p=0.036). Among excised lesions, five were of non-melanocytic origin in the TR group and nine in the TDS group (Table 2). In the TR group, five seborrheic keratoses were confirmed by partial biopsy, but none were considered high-priority (SC pathway) at in-person visits at the tertiary DU.

Statistics

Background characteristics are expressed as percentages of the total number of individuals or lesions observed, or mean values and 95% confidence intervals (CIs). Lead times were not normally distributed in the study population and are presented as medians with interquartile ranges (IQRs). P values were calculated with the two-sample Wilcoxon-Mann-Whitney rank-sum test or chi-squared test (dichotomous variables), and p < 0.05 was considered significant. All statistical calculations were performed with Stata statistical software (StataCorp 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Ethics

Ethical approval was obtained from the Swedish ethics committee (2019-01290).
### Table 1. Characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Traditional referral (n=66)</th>
<th>Teledermatoscopy (n=132)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean 61.0 95% CI 57.0–64.9</td>
<td>Mean 56.1 95% CI 53.4–58.9</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Female sex (%)</strong></td>
<td>Proportion 42.4 95% CI 30.3–55.2</td>
<td>Proportion 53.8 95% CI 44.9–62.5</td>
<td>0.132</td>
</tr>
<tr>
<td><strong>Proportion of melanoma</strong></td>
<td>54.5 95% CI 42.2–68.9</td>
<td>54.5 95% CI 45.9–63.2</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Proportion of in situ melanoma</strong></td>
<td>19.7 95% CI 10.9–31.3</td>
<td>34.1 95% CI 26.1–42.8</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Proportion of invasive melanoma</strong></td>
<td>34.8 95% CI 23.0–46.7</td>
<td>20.5 95% CI 13.5–27.4</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Thickness of invasive melanoma (mm)</strong></td>
<td>1.35 Mean 0.30–4.50</td>
<td>0.74 Mean 0.20–2.15</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Max lesion diameter (mm)</strong></td>
<td>11.4*** Mean 2–30</td>
<td>9.4*** Mean 2–30</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>Lesion localization</strong></td>
<td>Number Proportion (%)</td>
<td>Number Proportion (%)</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>8/66 12.1</td>
<td>10/132 7.6</td>
<td></td>
</tr>
<tr>
<td>Arms (including shoulders)</td>
<td>13/66 19.7</td>
<td>20/132 15.2</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>16/66 24.2</td>
<td>26/132 19.7</td>
<td></td>
</tr>
<tr>
<td>Trunk (including neck, gluteus)</td>
<td>29/66 43.9</td>
<td>76/132 57.6</td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval *Traditional referral: 66 lesions, 36 melanomas (13 in situ, 23 invasive). **Teledermatoscopy: 132 lesions, 72 melanomas (45 in situ, 27 invasive). ***There were missing values regarding diameter of the lesion: traditional referral group (n=6), teledermatoscopy group (n=3). P values calculated with the chi-squared test (dichotomous variables) or the two-sample Wilcoxon-Mann-Whitney rank-sum test. Significant differences marked in bold.

### Table 2. Diagnoses of the excised lesions (suspected malignant melanoma at first visit in primary care) among the study participants.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Traditional referral (N=66)</th>
<th>Teledermatoscopy (N=132)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Excised</strong></td>
<td><strong>Partial biopsy</strong></td>
<td><strong>Clinical evaluation</strong></td>
</tr>
<tr>
<td>Melanoma invasive</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Melanoma in situ</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe dysplastic nevus</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Melanocytic nevus</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spitzoid lesion</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other***</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Lesion evaluated as highly suspected malignant melanoma at face-to-face visit at a tertiary dermatology unit (n=53) ** Patient declined excision. *** Traditional referral group: Epidermal hyperplasia, angioma, lichenoid keratosis, paronychia, subungual bleeding, pseudocyst. Teledermatoscopy group: Atypical lentiginous lesion, lentigo benigna, lichenoid keratosis, angioma, fibrous histiocytoma, basal melanosis.
TR Group Analysis
Of the 66 patients with a referral from PCU, and labelled high-priority by a dermatology consultant, 56 were assessed as eligible for the SC pathway at an in-person visit at the tertiary DU. In ten cases, the SC pathway was aborted at in-person visits due to the lesion not meeting the criteria of suspected melanoma; one was of melanocytic origin (melanocytic nevus) and was excised, while the rest had other diagnoses. Three lesions were managed through partial biopsy at the first visit and not scheduled for diagnostic excision. In the TR group (n=53), median lead time from first visit at PCU to diagnostic excision was 10 days (IQR 6–20; mean 16.2). When excluding eight patients that were referred to a plastic surgery unit (SU), the median lead time was 10 days (IQR 6–14; mean 11.4).

TDS Group Analysis
Of 132 TDS referrals assessed as suspected melanoma, 128 were excised (Fig. 4). Excision was performed at PCU in 40 cases. Seventy-seven cases were referred to a dermatology unit (DU) for excision. In seven cases, the PCU chose to refer the patient to a plastic SU due to lesion location and size. Four lesions were referred to a general practice surgeon. Reasons for lesions not being excised (n=4): patients declined excision/further treatment (n=2), referral to a DU where another dermatologist ended the SC pathway, viewing the lesion as benign (n=1), lentigo maligna treated with Grenz rays [25] after biopsy instead of excision (n=1).

Median lead time from the first visit to diagnostic excision was 13 days (IQR 6–19; mean 15.7) among all excised lesions in TDS (n=128). One patient’s referral was neglected, with late management (time to excision 156 days); the case was described as an invasive melanoma in the pathology report. After exclusion of that case, median lead time was 13 days (IQR 6–19; mean 14.6). Some patients were rescheduled at the PCU visit and received a separate appointment for TDS (n=26), which resulted in extended lead time to diagnostic excision. Patients who got TDS at their first visit (n=101) had significantly shorter lead time (p<0.001) than those who were rescheduled: median 10 days (IQR 6–16; mean 12.6) vs. median 18 days (IQR 13–29; mean 22.3). Patients with a difficult site for excision of malignant melanoma were referred to a plastic surgeon (n=7). Median lead time for these patients was 25 days (IQR 16–43; mean 30.7). Patients with excision at other units (DU or general SU, n=80) had comparable lead times, median 13 days (IQR 8–17; mean 13.9). The median lead time for patients with surgery performed at a PCU (n=40) was significantly shorter (p=0.013) than for patients receiving surgery at other units, including plastic SU (n=87), 7.5 days (IQR 3–19.5, mean 13.2) vs. 13 days (IQR 8–19, mean 15.2).

Comparison of TR and TDS Group Lead Times
Including all excised SC pathway lesions in both cohorts (n=181), the median lead time from the first visit to diagnostic excision was 12 days (IQR 6–19; mean 15.8) and from referral to excision 10 days (IQR 6–16; mean 13.6).

Median lead times from first PCU visit to excision were comparable (p=0.657) between the TR group (n=53, 10 days, IQR 6–20; mean 16.2) and the TDS group (n=128, 13 days, IQR 6–19; mean 15.7). Median lead times from the date of referral sent from PCU to time of excision were also comparable (p=0.464): TR 10 days (n=53, IQR 6–20; mean 15.7) vs. TDS 9 days (n=128, IQR 5–15.5; mean 12.8).

When comparing the TR and TDS groups and excluding the neglected patient (lead time 156 days), times from the first visit to excision had a median of 10 vs. 13 days (p=0.716) and times from referral to excision were not significantly different (median 10 vs. 9 days, p=0.412). For histopathologically confirmed malignant melanomas, the median lead times from the first visit to excision were comparable (p=0.905) in the TR (n=36) and TDS groups (n=71): 13 days (IQR 6.5–22; mean 19.1) vs. 14 days (IQR 7–18; mean 16.8), as were the median lead times from referral to excision (p=0.166): TR 12.5 days (IQR 6–22; mean 18.4) vs. TDS 10 days (IQR 4–15; mean 13.2).

Discussion
In this study from Stockholm, patients with suspected malignant melanoma identified in PC had a median lead time of 12 days (IQR 6–19; mean 15.8) from first consultation to diagnostic excision. We found that the use of TDS referral pathways in PC was at least as efficient regarding lead time as TR to a well-organized hospital clinic specialized in cutaneous cancer care. The study identified an organizational procedure that prolonged the lead time when using TDS. If TDS were optimized by avoiding internal rescheduling for TDS at the PCU, it could have an even shorter lead time to excision. The impact of TDS on lead time might be of even greater value in rural areas. Furthermore, our findings showed that lead time in both cohorts was comparable to the standards recommended in international guidelines presented in the Australian Optimal Care Pathway for people with melanoma and the UK Government two-week rule for the skin cancer referral pathway [26,27]. The lead times in our study are favorable compared with those in other settings [16,17]. However, the Swedish SC pathway’s ideal time...
frame of seven days to excision was not achieved in either the TR or the TDS group. The shortest lead times were observed for patients with surgery performed at a PCU.

In our analyses of histopathologically confirmed malignant melanoma excised at a PCU (n=20), median time from referral for TDS to excision was 4 days (range 1–47) and from first PCU visit to excision 7.5 days (range 1–47). Similarly, Wikström et al. have recently shown that patients in Stockholm with malignant melanoma had a significantly shorter median lead time to diagnostic excision when surgery was performed by a general practitioner (GP) (5 days) when compared with private dermatology/surgery or university clinics (16 and 12 days, respectively) [28]. Both studies indicated that PC in Stockholm was more effective regarding lead time to excision than when patients were referred for excision. If TDS is used properly, the lead time to excision for patients with suspected malignant melanomas could be reduced even more. Other studies have shown that lead time can be reduced by using TDS [15-18,29]. As pointed out in the literature review by Finnane et al., actual waiting times vary significantly between different studies [14]. Congalton et al. demonstrated the ability of TDS to reduce wait times in a virtual lesion clinic (VLC), a skin imaging center, in New Zealand [16]. Patients were referred by a GP to a VLC, where TDS was performed. The median waiting time between referral and VLC assessment was 9 days, compared with 26.5 days for standard outpatient assessment by a dermatologist. VLC patients underwent excision earlier than patients undergoing a standard assessment. Median time to excision of a suspected melanoma was 40 days from VLC assessment. In another consecutive study from New Zealand, Sunderland et al. showed that a hybrid e-referral system, where an experienced surgical oncologist selected the management option or referred suspected melanomas for TDS, could reduce the number requiring excision [30]. In a TDS project in Belgium (Telespot), Damsin et al. found a median delay of 11 days between TDS diagnosis and treatment of high-priority lesions, which was seven times shorter than the conventional care pathway [17]. Morton et al. set up a photo triage center and reduced mean waiting times to intervention for melanoma from 39 to 36 days [29]. In both Congleton et al. and Morton et al., patients were lost to follow-up since they did not show up for the photo session (10% and 22%, respectively). This highlights why TDS at a first visit is important, and when TDS is performed at the first PCU visit, the risk of no-shows can be eliminated.

Studies on the timeline from a patient first noticing a lesion to consultation and excisional biopsy have not shown any impact on Breslow thickness, though they have shown that patient delay (pre-presentation time) makes up the largest proportion of the delay [31,32]. There are studies indicating that time to excision can affect the prognosis, at least for nodular melanomas: five- and ten-year disease-specific survival both decreased by 14.4% in patients treated after a potential delay of 3 months [33]. Radical diagnostic excision is probably the most important therapeutic intervention in a localized disease stage, and studies on time to subsequent wide excision have reported somewhat contradictory outcomes on prognosis [34,35]. The need of improving the prevention and outcomes of skin cancer is discussed in the summary by Garbe et al. [36]. They highlight that better training of GPs/PC physicians in skin cancer detection and better coordination of the patient care pathway from the GP/PC physician are necessary. The threshold for patients seeking help for a worrisome skin lesion may be reduced by convenient, easily accessible, well-organized expertise – for instance through TDS – in PC. We observed that PC physicians initially referred banal lesions for TDS evaluation, but this gradually advanced to predominantly complex referrals. As discussed in the review of Fee et al., one of the barriers to the use of dermatoscopy in PC is lack of training [37]. The educational value of TDS in PC could be significant and is not well-studied. Furthermore, TDS is still not included in European residency programs. To date, some TDS projects were carried out, for training purposes (i.e., early melanoma recognition) and showed that residents/novices reached a higher learning curve and accuracy compared with older experts, especially with mobile tools [38,39]. In addition, the covid pandemic has stressed the importance of being able to manage TDS tools.

The use of dermatoscopy by general practitioners in conjunction with the value of TDS could significantly improve the early detection of melanoma. It may, in part, explain the detection of a higher proportion of in situ melanomas and melanomas with a lower Breslow thickness in the TDS cohort. Further, there is evidence that melanomas detected by dermatologists are thinner than those detected by non-dermatologists [40]. An alternative explanation is the involvement of selection bias where the more obvious melanomas are referred to either a dermatologist or for excision (without TDS consultation), while PCUs use TDS for more equivocal lesions. If this is true, then the number needed to excise for benign lesions may decrease with TDS.

This paper compares two ways of processing patients with suspected melanoma lesions, initially evaluated in PC. We did not find any significant difference in lead times between the TR pathway and the TDS pathway. When analyzing teledermatoscopy separately, we could conclude that there was potential to optimize lead times by using TDS at a first appointment, rather than rescheduling specifically for TDS – and also, when possible, performing diagnostic excision in a PCU. In Stockholm, TDS is becoming one of the key instruments in PC, with PC physicians enlisting the aid of dermatology specialists. Although studies have recognized
that TDS can be an effective tool to improve skin cancer care, research has yet to closely investigate its role in varied settings, such as urban or rural.

**Strengths and Limitations**

The major strengths of this study are the cohort design and the inclusion of a cohort of patients treated with standard healthcare (TR group) for comparison of lead times. However, it is a limitation that we included only one tertiary center, making it difficult to generalize our findings to healthcare systems in other settings, such as other regions in Sweden, remote or rural areas, or other countries with unstructured tracking of suspicious cancer. Another limitation is that the study was conducted at the time of a pilot TDS project, and therefore not representative of how efficient it will be after implementation.

**Conclusions**

Lead time from a first PCU visit to diagnostic excision in a TDS urgent referral pathway in PC was comparable to that of a traditional urgent referral pathway to a well-organized hospital clinic. If TDS is used at the first PC consultation, the lead time to diagnostic excision of suspected melanomas could be shorter than it is with the standard referral pathway.

**References**


The Psychosocial Impact of Chronic Facial Dermatoses in Adults

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Key words: acne, anxiety, depression, rosacea, seborrheic dermatitis

Citation: Ozcan Y, Sungur MA, Yaman Ozcan B, Eyup Y, Ozlu E. The Psychosocial Impact of Chronic Facial Dermatoses in Adults. Dermatol Pract Concept. 2023;13(1):e2023029. DOI: https://doi.org/10.5826/dpc.1301a29

Accepted: April 16, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Skin diseases have negative psychological and social consequences, especially when they are chronic and affect a visible area of the body, such as the face.

Objectives: The purpose of this study is to investigate and compare the psychosocial impact of three common chronic dermatoses of the face: acne, rosacea, and seborrheic dermatitis.

Methods: The Dermatology Life Quality Index (DLQI), Hospital Anxiety and Depression Scale (HADS), and Social Appearance Anxiety Scale (SAAS) were used to compare acne, rosacea, and seborrheic dermatitis patients and healthy controls. The relationships between DLQI, HADS, and SAAS results were investigated, as well as their associations with disease duration and severity.

Results: The study included 166 acne patients, 134 rosacea patients, 120 seborrheic dermatitis patients, and 124 controls. The patient groups had significantly higher DLQI, HADS, and SAAS scores than the control group. Rosacea patients had the highest DLQI and SAAS scores, as well as the highest anxiety prevalence. Patients with seborrheic dermatitis had the highest rate of depression. The DLQI, HADS, and SAAS results were moderately correlated with each other, but their relationship with disease duration and severity was insignificant or weak at best.

Conclusions: Chronic facial dermatoses have a detrimental impact on mood and quality of life. Although patients with acne, rosacea, and seborrheic dermatitis have distinct lesions, the outcomes in terms of quality of life, anxiety, and depression are largely similar. Furthermore, these patients report similar levels of social anxiety as a result of their overall appearance.
Introduction

Healthy skin shields the organism from the outside. However, in its absence, a person becomes not only vulnerable to the physical environment but also suffers from psychological and social problems. While it is easier to conceal pathologies in certain areas, concealing the face is often more difficult. One’s social, economic, and romantic opportunities are shaped by one’s face. Thus, facial dermatoses may be more likely to have negative consequences.

Acne, rosacea, and seborrheic dermatitis are chronic skin diseases that primarily affect the face. Although each of these diseases is well known to be associated with poor quality of life, anxiety, and depression, no study has been conducted to compare the psychosocial burden of these diseases.

In this study, we examined acne, rosacea, or seborrheic dermatitis patients who presented to a dermatology outpatient clinic with facial complaints. We hoped to use the findings to better identify patients who might benefit from psychosocial support in addition to dermatological care, as well as to strengthen patient compliance. The patients’ quality of life as well as the frequency and severity of anxiety and depression were compared. Also, the social anxiety caused by patients’ overall appearances—which extended beyond their facial appearance—was compared.

Objectives

The purpose of this study was to compare the quality of life, anxiety, and depression levels in adult acne, rosacea, and seborrheic dermatitis patients and healthy controls. We also compared the social anxiety caused by overall appearance (rather than just the face) between these groups.

Methods

Study Design, Participants and Ethics

This cross-sectional study included patients between the ages of 18 and 65 who presented to the Duzce University Hospital Dermatology Clinic with acne, rosacea, or seborrheic dermatitis between October 2020 and July 2021. Patients who presented with more than one of these diagnoses, as well as patients with other facial dermatoses, scarring, or dysmorphia, were excluded from the study. Patients who were pregnant or breastfeeding, patients with comorbidities that could cause neurological or psychiatric symptoms, and those who had used central nervous system-influencing medications in the previous 6 months (including systemic isotretinoin) were all excluded from the study. Hospital employees were chosen as healthy controls.

The study protocol was reviewed and approved by the Duzce University Ethics Committee (07.09.2020–2020/199). All participants in the study provided written consent.

Sociodemographic and Clinical Characteristics

All participants’ ages, genders, and BMIs, as well as the severity and duration of illness for patient groups, were recorded. Global acne grading system[1] for acne patients, rosacea clinical scorecard[2] for rosacea patients, and seborrheic dermatitis area severity index[3] for seborrheic dermatitis patients were used to assess the severity of illness, and only the scores obtained from the facial area were used.

The Dermatology Quality of Life Index (DQLI)

This scale, created by Finlay[4] and adapted by Ozturkcan[5], aims to measure and compare data across all skin diseases. Questions are answered based on the previous week. The higher the final score, the greater the decrease in quality of life. The outcomes are graded as follows:

- 0 – 1 no effect at all on patient’s life
- 2 – 5 small effect on patient’s life
- 6 – 10 moderate effect on patient’s life
- 11 – 20 very large effect on patient’s life
- 21 – 30 extremely large effect on patient’s life

It is further divided into six subscales to determine the focus of the impact on quality of life:

- Questions 1&2: Symptoms, feelings
- Questions 3&4: Daily activities
- Questions 5&6: Leisure
- Question 7: Work/school
- Questions 8&9: Personal relationships
- Question 10: Treatment

The Hospital Anxiety and Depression Scale (HADS)

The hospital anxiety and depression scale was created to screen for the presence of anxiety and depression in patients with physical illnesses who presented to non-psychiatric clinics[6]. Half of the 14-question scale investigates anxiety, while the other half investigates depression. It is answered based on the previous week. In 1993, Aydemir et al. adapted it, and cut-off scores indicating the presence of anxiety and depression were determined[7]. An anxiety subscale score of 11 or higher indicates the presence of anxiety, whereas a depression subscale score of 8 or higher indicates the presence of depression[7]. The results also reflect the severity of anxiety and depression, allowing them to be used in comparisons or patient follow-up[6].

The Social Appearance Anxiety Scale (SAAS)

The social appearance anxiety scale was developed by Hart et al. in 2008[8] and later adapted by Dogan et al. in 2010[9]. It was created to assess fear in situations where the person’s
The overall external appearance can be evaluated. The appearance is assessed in a broader context, rather than focusing on a specific feature such as hair, nose, or chest size. Its primary purpose is to assess the components of social anxiety. The scale consists of 16 questions with no cut-off point. As the score rises, so does the person’s anxiety about his or her appearance.

**Statistics**

Baseline demographic and clinical characteristics in acne, rosacea, seborrheic dermatitis, and control groups were described using mean (standard deviation), median (interquartile range), frequencies, and percentages. The Pearson chi-square test was used to compare the categorical variable (sex). The continuous variables (age, BMI, and duration of illness) were initially evaluated using the Kolmogorov-Smirnov test, and then compared using the Kruskal-Wallis test because they did not have a normal distribution. Pairwise comparisons were analyzed using the Mann-Whitney U test with Bonferroni correction.

The distribution of the DLQI, HADS, and SAAS results in the acne, rosacea, seborrheic dermatitis, and control groups was analyzed using the Kolmogorov-Smirnov test. Because the data did not have a normal distribution, the Kruskal-Wallis test was performed to compare the results. Pairwise comparisons were analyzed using the Mann-Whitney U test, with Bonferroni correction applied in cases where the difference was found to be significant. Furthermore, Quade’s non-parametric analysis of covariance (ANCOVA) was employed to account for differences in baseline demographic factors, including age, gender, and BMI.

Scheffé’s method was employed as a post-hoc test. Categorical variables were evaluated using Pearson’s chi-square, Fisher’s exact test, or Fisher-Freeman-Halton test, depending on the expected value principle. Pearson or Spearman correlation analysis was used to examine correlations between continuous variables, depending on the distribution of the data.

An ordinal logistic regression model was designed to analyze the relationship between acne, rosacea, seborrheic dermatitis, control groups, and DLQI outcomes using the previously described five outcome grades of the scale. For SAAS, an ordinal logistic regression model was also created, and the final scale score was employed as the response variable. The binary logistic regression models for anxiety and depression subscales were created using the previously defined cut-off values. The healthy controls served as the reference group. Age, gender, and BMI were included as covariates in all regression models, and the results were reported as adjusted odds ratios with 95% confidence intervals. The SPSS 26.00 package program was used to analyze the data. Statistical significance was defined as .05 or less.

**Results**

**Participants**

The study enrolled 166 acne, 134 rosacea, and 120 seborrheic dermatitis patients, along with 124 healthy volunteers. Rosacea patients had the highest mean age, BMI, and longest duration of illness. Acne patients had the lowest mean age of any group. The majority of patients with acne and rosacea were female, while the majority of patients with seborrheic dermatitis were male (Table 1).

| Table 1. The baseline demographic and clinical features of the participants. |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
|                                | Acne           | Rosacea        | Seborrheic Dermatitis | Control        | p               |
| **n (%)**                      | 166 (30.5)     | 134 (24.6)     | 120 (22.1)            | 124 (22.8)     | —               |
| **Age**                        |                |                |                    |                |                |
| Mean (SD)                      | 22.8 (5.3)     | 37.9 (12.9)    | 31.9 (12.2)          | 31.7 (11.1)    | < .001*     |
| Median (IQR)                   | 21.5 (6)       | 36 (22)        | 28 (13)              | 27.5 (15)      |                |
| [Min.–Max.]                    | [18–55]        | [18–65]        | [18–65]              | [20–65]        |                |
| **Sex, n (%)**                 |                |                |                    |                |                |
| Male                           | 51 (30.7)      | 29 (21.6)      | 89 (74.2)            | 64 (51.6)      | < .001**    |
| Female                         | 115 (69.3)     | 105 (78.4)     | 31 (25.8)            | 60 (48.4)      |                |
| **BMI**                        |                |                |                    |                |                |
| Mean (SD)                      | 22.3 (3.4)     | 28.8 (6.1)     | 25.3 (4.7)           | 24.8 (4.5)     | < .001*     |
| Median (IQR)                   | 21.6 (4)       | 28 (7.5)       | 24.6 (6.1)           | 24.4 (6.6)     |                |
| [Min.–Max.]                    | [16–40.4]      | [17.5–53.1]    | [15.4–39.4]          | [16.4–41.5]    |                |
| **Duration of Illness**, Years |                |                |                    |                |                |
| Mean (SD)                      | 4.7 (4.1)      | 8.4 (9.5)      | 4.9 (6.5)            | 0              | .003*        |
| Median (IQR)                   | 4 (4.5)        | 5 (10)         | 3 (5)                | 0              |                |
| [Min. – Max.]                  | [0 – 20]       | [0 – 40]       | [0 – 50]             | 0              |                |

*Kruskal-Wallis test
**Pearson Chi-square
Pairwise comparisons are significant at p < .05 for:
1 Acne vs. Rosacea, Seborrheic dermatitis, Control; Rosacea vs. Seborrheic dermatitis, Control
2 Acne vs. Rosacea; Rosacea vs. Seborrheic dermatitis
The Dermatology Life Quality Index
Acne, rosacea, and seborrheic dermatitis patients (p <.001) had a significantly lower quality of life than the control group when the results were interpreted as grades (Figure 1). The negative impact on quality of life was similar across acne, rosacea and seborrheic dermatitis patients.

Acne patients had a higher mean and median score than seborrheic dermatitis patients and a lower mean and median score than rosacea patients [DLQI, mean (SD) = acne: 5.5 (5.1); rosacea: 6.3 (5.8); seborrheic dermatitis: 4.3 (4); control: 1.3 (1.8)]. The only statistically significant difference after adjusting for age, gender, and BMI was found in pairwise comparisons between the patient groups and the healthy controls (Table 2).

Acne patients had higher average scores on the “symptoms and feelings” and “treatment” subscales, whereas rosacea patients had higher impairment in “daily activities,” “leisure,” “work and school,” and “personal relationships.” But the only significant result was obtained when comparing patients with rosacea and seborrheic dermatitis on the subscale concerning daily activities (mean (SD): rosacea: 1.13 (1.6) – seborrheic dermatitis: .48 (.92); p = .002).

Ordinal logistic regression was performed to evaluate the likelihood of being in a higher DLQI grade in acne, rosacea, and seborrheic dermatitis patients, with healthy controls serving as the reference group. Age, gender, and BMI were identified as confounders and were adjusted for. The logistic regression model was statistically significant [$\chi^2(6) = 134.513$, p <.001]. The adjusted odds ratio for acne patients was 8.78 (95% CI 5.24–14.72, p <.001), for rosacea patients was 13.04 (95% CI 7.44–22.86, p <.001), and for the seborrheic dermatitis patients was 8.17 (95% CI 4.80–13.88, p <.001).

The Hospital Anxiety and Depression Scale
HADS results suggested the presence of anxiety in 30 (18.1%) acne patients, 50 (37.3%) rosacea patients, 31 (25.8%) seborrheic dermatitis patients, and 10 (8.1%) subjects from the control group (Table 3). Using the previously reported cut-off points in the HADS, a binary logistic regression model was used to investigate the relationship between the acne, rosacea, seborrheic dermatitis, and control groups, and the presence of anxiety. Age, gender, and BMI were identified as confounders and were adjusted for. The healthy controls served as the reference group. The logistic regression model was statistically significant [$\chi^2(6) = 37.542$, p <.001]. The presence of anxiety was associated with an adjusted odds ratio of 2.59 (95% CI 1.18–5.69, p =.017) in acne patients, 5.90 (95% CI 2.73–12.73, p <.001) in rosacea patients, and 4.01 (95% CI 1.84–8.73, p <.001) in seborrheic dermatitis patients.

In terms of anxiety severity, patients with rosacea scored the highest, with a mean of 8.49 (4.7). Seborrheic dermatitis patients had a mean of 7.92 (4.19), acne patients had a mean of 7.32 (3.99), and the control group had a mean of 5.73 (3.52). After controlling for age, gender, and BMI, we discovered that...
In rosacea patients, and 3.53 (95% CI 1.89–6.59, p <.001) in seborrheic dermatitis patients.

In terms of depression severity, rosacea patients received the highest scores, with a mean of 6.51 (3.73). This was followed by seborrheic dermatitis with a mean of 6.31 (3.62), acne with a mean of 5.66 (3.54), and the control group with a mean of 4.59 (2.89). After controlling for age, gender, and BMI, it was found that acne, rosacea, and seborrheic dermatitis patients experienced more severe depression than healthy controls, but there was no significant difference between the patient groups (Table 3).

The depression subscale suggested the presence of depression in 46 (27.7%) of the acne patients, 51 (39.5%) of the rosacea patients, 49 (41.5%) of the seborrheic dermatitis patients, and 19 (16.1%) of the control group (Table 3). To examine the association between the acne, rosacea, seborrheic dermatitis, and control groups and the presence of depression, a binary logistic regression model was created using the depression cut-off points in the HADS. Age, gender, and BMI were identified as confounders and were adjusted for. The healthy controls served as the reference group. The logistic regression model was statistically significant \( \chi^2(6) = 25.227, p <.001 \). The presence of depression was associated with an adjusted odds ratio of 2.16 (95% CI 1.15–4.04, \( p = .016 \)) in acne patients, 3.35 (95% CI 1.89–6.59, \( p <.001 \)) in rosacea patients, and 3.53 (95% CI 1.89–6.59, \( p <.001 \)) in seborrheic dermatitis patients.

In terms of depression severity, rosacea patients received the highest scores, with a mean of 6.51 (3.73). This was followed by seborrheic dermatitis with a mean of 6.31 (3.62), acne with a mean of 5.66 (3.54), and the control group with a mean of 4.59 (2.89). After controlling for age, gender, and BMI, it was found that acne, rosacea, and seborrheic dermatitis patients experienced more severe depression than healthy controls, but there was no significant difference between the patient groups (Table 3).

The Social Appearance Anxiety Scale
According to the results of the SAAS, rosacea patients had the highest mean score of 38.51 (16.37). Acne patients had a mean of 36.86 (14.24), seborrheic dermatitis patients had a mean of 33.83 (13.67), and the control group had a mean of

Table 2. Comparison of dermatology life quality index (DLQI) scores by group.

<table>
<thead>
<tr>
<th></th>
<th>Acne</th>
<th>Rosacea</th>
<th>Seborrheic Dermatitis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>4 (5)</td>
<td>5 (7)</td>
<td>3 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Min.-Max.</td>
<td>[0-26]</td>
<td>[0-27]</td>
<td>[0-16]</td>
<td>[0-10]</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.5 (5.1)</td>
<td>6.3 (5.8)</td>
<td>4.3 (4)</td>
<td>1.3 (1.8)</td>
</tr>
<tr>
<td>SEM</td>
<td>.399</td>
<td>.501</td>
<td>.372</td>
<td>.165</td>
</tr>
<tr>
<td>( p^* )</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

\( p \) value for Kruskal-Wallis test < .001
* Mann-Whitney U test.
After controlling for age, gender, and BMI, pairwise comparisons are significant (\( p <.05 \)) for:
Acne vs. Control; Rosacea vs. Control; Seborrheic dermatitis vs. Control.

Table 3. Comparison of the frequency and severity of anxiety and depression by group.

<table>
<thead>
<tr>
<th></th>
<th>Acne</th>
<th>Rosacea</th>
<th>Seborrheic Dermatitis</th>
<th>Control</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n (%)</td>
<td>166 (30.5)</td>
<td>134 (24.6)</td>
<td>120 (22.1)</td>
<td>124 (22.8)</td>
<td></td>
</tr>
<tr>
<td>Anxiety, n (%)</td>
<td>30 (18.1)</td>
<td>50 (37.3)</td>
<td>31 (25.8)</td>
<td>10 (8.1)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Median (IQR) [Min.-Max.]</td>
<td>7 (5) [0-19]</td>
<td>9 (7) [0-19]</td>
<td>7 (6) [0-19]</td>
<td>6 (4) [0-20]</td>
<td>&lt; .001**</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.32 (3.99)</td>
<td>8.49 (4.7)</td>
<td>7.92 (4.19)</td>
<td>5.73 (3.52)</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>.31</td>
<td>.407</td>
<td>.382</td>
<td>.317</td>
<td></td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>46 (27.7)</td>
<td>51 (39.5)</td>
<td>49 (41.5)</td>
<td>19 (16.1)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Median (IQR) [Min.-Max.]</td>
<td>5 (5) [1 – 18]</td>
<td>6 (5) [0 – 19]</td>
<td>6 (6) [0 – 14]</td>
<td>4 (4) [0 – 14]</td>
<td>&lt; .001**</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.66 (3.54)</td>
<td>6.51 (3.73)</td>
<td>6.31 (3.62)</td>
<td>4.59 (2.89)</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>.275</td>
<td>.323</td>
<td>.331</td>
<td>.260</td>
<td></td>
</tr>
</tbody>
</table>

\( * \) Pearson Chi-square
** Kruskal-Wallis test
After controlling for age, gender, and BMI, pairwise comparisons are significant (\( p <.05 \)) for:
Anxiety: Acne vs. Control; Rosacea vs. Control; Seborrheic dermatitis vs. Control.
Depression: Acne vs. Control; Rosacea vs. Control; Seborrheic dermatitis vs. Control.

patients with acne, rosacea, and seborrheic dermatitis experienced more severe anxiety than healthy controls, but there was no significant difference across the patient groups (Table 3).
26.37 (8.4). In paired comparisons, acne, rosacea, and seborrheic dermatitis patients’ scores were significantly higher than the control group after controlling for age, gender, and BMI. The pairwise comparisons of the patient groups revealed no significant differences (Table 4).

An ordinal logistic regression model was created to explore the relationship between the acne, rosacea, seborrheic dermatitis, and control groups and the SAAS results. Age, gender, and BMI were identified as confounders and were adjusted for. The healthy controls served as the reference group. The logistic regression model was statistically significant \[\chi^2(6) = 54.586, p < .001\]. The adjusted odds ratio for receiving a higher score on the scale was 3.14 (95% CI 2.05–4.81, \(p < .001\)) for acne patients, 4.05 (95% CI 2.54–6.48, \(p < .001\)) for rosacea patients, and 2.46 (95% CI 1.57–3.83, \(p < .001\)) for seborrheic dermatitis patients.

**Correlations**

There was a positive relationship between disease severity and the DLQI, HADS, and SAAS scores in acne and rosacea patients. Similarly, a positive relationship was found between disease severity and the DLQI and SAAS scores in patients with seborrheic dermatitis. These associations were found to be significant but weak, with the strongest link being found between the severity of seborrheic dermatitis and the DLQI results \([r_{120} = .446, p = .000]\). There was no significant relationship between illness duration and DLQI, HADS, or SAAS outcomes in the patient groups (Table 5).

In all patient groups, the DLQI, HADS, and SAAS outcomes had significant and positive correlations with each other (Table 6). The strongest correlation was seen between the HADS anxiety and depression subscales, which were moderately correlated with each other. There was also a moderate association between the DLQI and the SAAS outcomes in acne patients \([r_{166} = .659, p = .000]\).

**Discussion**

Acne, rosacea, and seborrheic dermatitis patients’ quality of life was found to be significantly lower when compared to healthy people. These patients reported having more negative feelings about themselves as a result of their skin illnesses, and they had more difficulty with their daily and leisure time activities, work and school lives, and personal relationships.

### Table 4. Comparison of social appearance anxiety scale (SAAS) scores between groups.

<table>
<thead>
<tr>
<th></th>
<th>Acne</th>
<th>Rosacea</th>
<th>Seborrheic Dermatitis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>35 (22)</td>
<td>35 (26)</td>
<td>32 (23)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>[Min.-Max.]</td>
<td>[16 – 75]</td>
<td>[16 – 79]</td>
<td>[16 – 67]</td>
<td>[16 – 50]</td>
</tr>
<tr>
<td>Mean</td>
<td>36.86 (14.24)</td>
<td>38.51 (16.37)</td>
<td>33.83 (13.67)</td>
<td>26.37 (8.4)</td>
</tr>
<tr>
<td>SEM</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.754</td>
</tr>
</tbody>
</table>

\(p^*\) value for Kruskal-Wallis test < .001
* Mann-Whitney U test.

After controlling for age, gender, and BMI, pairwise comparisons are significant \(p < .05\) for:
Acne vs. Control; Rosacea vs. Control; Seborrheic dermatitis vs. Control.

### Table 5. The correlations between severity and duration of illness with the dermatology quality of life index, anxiety and depression scores, and the social appearance anxiety scale in patient groups.

<table>
<thead>
<tr>
<th>Severity of Illness</th>
<th>DLQI</th>
<th>Anxiety Subscale</th>
<th>Depression Subscale</th>
<th>SAAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>.271**</td>
<td>.172*</td>
<td>.206*</td>
<td>.241*</td>
</tr>
<tr>
<td>Rosacea</td>
<td>.354**</td>
<td>.290**</td>
<td>.272*</td>
<td>.308**</td>
</tr>
<tr>
<td>Seborrheic Dermatitis</td>
<td>.446**</td>
<td>.173</td>
<td>.198</td>
<td>.262*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Illness</th>
<th>DLQI</th>
<th>Anxiety Subscale</th>
<th>Depression Subscale</th>
<th>SAAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>-.022</td>
<td>.071</td>
<td>-.002</td>
<td>-.007</td>
</tr>
<tr>
<td>Rosacea</td>
<td>-.144</td>
<td>-.108</td>
<td>-.122</td>
<td>.003</td>
</tr>
<tr>
<td>Seborrheic Dermatitis</td>
<td>-.053</td>
<td>.018</td>
<td>-.036</td>
<td>.070</td>
</tr>
</tbody>
</table>

DLQI: Dermatology Life Quality Index, SAAS: Social Appearance Anxiety Scale, \(r\): Correlation coefficient.
* significant at \(p < .05\)
** significant at \(p < .001\)
triggers such as the sun, weather, stress, emotional state, and various foods may cause patients to develop an avoidance behavior, either consciously or unconsciously. Patients may refrain from participating in outdoor activities to avoid being exposed to triggers such as the sun, hot or cold air, wind, and social gatherings to avoid emotional triggers. This can result in introversion, social isolation, depression, and anxiety. A lack of sunlight is linked to an increased risk of depression[12,13]. Anxiety and other psychological stressors contribute to this cycle by exacerbating rosacea symptoms through the release of proinflammatory cytokines[14].

Another intriguing finding is the high rate of depression in seborrheic dermatitis patients. Seborrheic dermatitis is frequently linked to neurological conditions such as Parkinson’s disease[15,16], tardive dyskinesia[17], or spinal damage[18]. There is also a link between seborrheic dermatitis and psychiatric illnesses. According to the literature, those with mood disorders are more likely to develop seborrheic dermatitis[19], and those with seborrheic dermatitis are more likely to develop depression[20]. Parkinson’s disease is characterized by a decrease in dopamine, and dopamine receptor blockage results in tardive dyskinesia. Recently, the importance of dopamine has been emphasized in addition to serotonin and noradrenaline in the pathophysiology of depression[21]. Although our study was observational in nature and was not intended to establish a cause-effect relationship, it is worth noting that seborrheic dermatitis is frequently seen in conjunction with diseases in which dopamine plays a prominent role in the pathophysiology.

Our findings show that the severity of psychosocial impact in patients with acne, rosacea, and seborrheic dermatitis is unrelated to the duration or severity of symptoms. The literature shows that even when different measurement methods are used, the results are similar. Acne[22,23], rosacea[24,25], and seborrheic dermatitis[26] severity and duration have been reported to be insignificant or significant but.

Furthermore, anxiety and depression were both more common and severe in these individuals. They experienced more intense social anxiety as a result of their beliefs that their appearance would be judged negatively, and the source of this anxiety extended beyond the facial area to overall negative body image thoughts (not being attractive, being overweight, hair color, nose shape, body shape).

Rosacea patients had the most negative impact on their quality of life, followed by acne and seborrheic dermatitis patients, respectively. There was also a statistically significant difference between rosacea and seborrheic dermatitis patients. This difference, however, was eliminated after controlling for age, sex, and BMI. Similarly, the severity of social anxiety caused by overall appearance was highest in rosacea patients, second in acne patients, and third in seborrheic dermatitis patients, but the differences were not statistically significant.

A study comparing acne and seborrheic dermatitis found that acne patients had a higher rate and severity of anxiety and depression[10]. A study in Lithuania comparing acne and rosacea patients aged 18-70 found that acne patients had higher anxiety and rosacea patients had higher depression[11]. The fact that these studies were completed with a smaller number of patients is a limitation. Our study included a larger number of participants, comparing patients with acne, rosacea, and seborrheic dermatitis simultaneously. According to our data, anxiety rates were highest in rosacea patients, followed by seborrheic dermatitis and acne patients, respectively. Depression rates were highest in patients with seborrheic dermatitis, followed by rosacea and acne patients, respectively. The severity of anxiety and depression, on the other hand, was comparable in acne, rosacea, and seborrheic dermatitis patients after controlling for age, sex, and BMI.

Rosacea patients’ physical symptoms, such as burning, stinging, redness, and flushing, may explain why the negative impact on quality of life is greater. Common rosacea triggers such as the sun, weather, stress, emotional state, and various foods may cause patients to develop an avoidance behavior, either consciously or unconsciously. Patients may refrain from participating in outdoor activities to avoid being exposed to triggers such as the sun, hot or cold air, wind, and social gatherings to avoid emotional triggers. This can result in introversion, social isolation, depression, and anxiety. A lack of sunlight is linked to an increased risk of depression[12,13]. Anxiety and other psychological stressors contribute to this cycle by exacerbating rosacea symptoms through the release of proinflammatory cytokines[14].

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Our findings show that the severity of psychosocial impact in patients with acne, rosacea, and seborrheic dermatitis is unrelated to the duration or severity of symptoms. The literature shows that even when different measurement methods are used, the results are similar. Acne[22,23], rosacea[24,25], and seborrheic dermatitis[26] severity and duration have been reported to be insignificant or significant but.

### Table 6. Correlations of the dermatology quality of life index, anxiety and depression scores, and the social appearance anxiety scale by groups.

<table>
<thead>
<tr>
<th></th>
<th>DLQI and Anxiety Subscale</th>
<th>DLQI and Depression Subscale</th>
<th>DLQI and SAAS</th>
<th>Anxiety and Depression Subscales</th>
<th>Anxiety Subscale and SAAS</th>
<th>Depression Subscale and SAAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>.468**</td>
<td>.473**</td>
<td>.659**</td>
<td>.564**</td>
<td>.413**</td>
<td>.339**</td>
</tr>
<tr>
<td>Rosacea</td>
<td>.354**</td>
<td>.338**</td>
<td>.487**</td>
<td>.671**</td>
<td>.400**</td>
<td>.437**</td>
</tr>
<tr>
<td>Seborrheic</td>
<td>.275*</td>
<td>.182*</td>
<td>.401**</td>
<td>.593**</td>
<td>.304**</td>
<td>.374**</td>
</tr>
<tr>
<td>Dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>.255*</td>
<td>.204*</td>
<td>.154</td>
<td>.330**</td>
<td>.333**</td>
<td>.039</td>
</tr>
</tbody>
</table>

DLQI: Dermatology Life Quality Index, SAAS: Social Appearance Anxiety Scale, r: Correlation coefficient.

* significant at p < .05
** significant at p < .001
weakly related to psychosocial outcomes. This suggests that patients with a new-onset or mild disease may be severely impacted. On the other hand, despite having a severe or long-term disease, some patients can maintain their mental health. This implies that what matters is not the biological process itself, but the meaning ascribed to one’s own illness.

Another intriguing aspect is the correlation between the DLQI, HAD, and SAAS results. The negative effects observed by these scales are significantly related to each other in all patient groups, with anxiety and depression having the most pronounced relationship. Mental symptoms caused by a physical illness, particularly chronic diseases, can lead to other mental problems and loss of function over time. Yazici et al. used the same measurement methods in their study on acne patients and found results that were similar to ours in terms of the relationship between quality of life and anxiety and depression[27].

Because of the nature of observational studies, cause-and-effect relationships cannot be established, and results may differ across cultures, time periods, or measurement methods. Furthermore, some selection bias is unavoidable, particularly when recruiting the control group. Therefore, we concentrated mostly on comparing patient groups to one another. The patient groups are made up of those who sought treatment, and it is reasonable to assume that those who have been severely impacted by the negative psychological and social consequences will seek treatment more frequently. As a result, those who have the disease but lack the motivation to seek treatment might be underrepresented in the study. Therefore, we can speculate that if similar studies were conducted with a general population sample, the psychosocial impact on the subjects would be less severe.

Acne, rosacea, and seborrheic dermatitis lead to a number of psychosocial consequences, but also vice versa. Sebocytes, which play a key role in the pathogenesis of acne, have functional receptors for molecules involved in the stress response, such as CRH, melanocortin, beta-endorphin, vasoactive intestinal polypeptide, neuropeptide Y, and calcitonin gene-related peptide[28]. It has been established that stress-induced reactive oxygen derivatives, antimicrobial peptides, and neuropeptides cause inflammation by activating various cytokine and chemokine networks in the formation of rosacea’s characteristic histopathology[29]. Observational studies have shown that patients with seborrheic dermatitis have more frequent and severe attacks during stressful times[30,31]. Breaking the disease-stress cycle in both steps may improve treatment outcomes.

A thorough skin examination should be complemented by a brief assessment of the patient’s mental state. Chronic skin diseases impose a significant psychosocial burden, which may be exacerbated if they are visible to others. Stress is not only a symptom of illness; it is also one of its causes, and it can lead to suicidal ideation during vulnerable times in one’s life. Identifying vulnerable patients and breaking the disease-stress cycle in both steps might improve patient compliance and treatment efficacy.

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The Relationship Between ABO and Rh Blood Groups with Alopecia Areata

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Key words: alopecia areata, blood group, ABO, Rh

Introduction: Alopecia areata (AA) is a common non-scarring hair loss disease. Genetic susceptibility and environmental factors can develop the disease.

Objectives: We investigated the association between AA and ABO and Rh blood groups.

Methods: This cross-sectional study was done on 200 patients with AA and 200 healthy controls (HCs) between March 2021 and September 2021.

Results: The prevalence of blood groups O, A, B, and AB in patients with AA was 30%, 30.5%, 10.5%, and 29%, respectively. A significant difference was detected between the two groups in the frequency of the ABO and ABO* Rh blood groups (p-value < 0.05). Compared to the HCs, the prevalence of the AB and AB+ blood group was higher in AA patients. No significant relationship was detected between sex, BMI, duration of disease, age at onset, severity of alopecia tool (SALT) score, hair loss pattern, and nail involvement with ABO and Rh blood groups (p-value > 0.05).

Conclusion: In conclusion, the highest difference was related to the AB+ blood group, so compared to HCs, the AB+ blood group frequency was higher in patients with AA. However, more studies with larger sample sizes on different ethnicities should be performed to verify the results of this study.
Introduction

Alopecia areata (AA) is a common non-scarring hair loss disorder. The prevalence of the disease is 1 in 1000 cases and has a lifetime incidence of 2% [1]. The prevalence of the disorders indicated above is expected to be roughly 0.2 percent in the overall population. Moreover, genetic susceptibility and environmental factors can also induce the disease to develop [2]. However, the specific cause of the disease is unidentified. There are several lines of evidence linking AA to autoimmune diseases, like type 1 diabetes mellitus (DM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), vitiligo, and pemphigus Vulgaris [3-6].

Human gene variation, such as HLA systems, is defined by red cell isoenzymes, blood groups, hemoglobin variations, and serum proteins [7]. The ABO blood group system includes four O, A, B, and AB common blood groups. The presence of specific carbohydrate sugars on the surface of red blood cells distinguishes these different blood groups. A is identified by N-acetylgalactosamine, and B is identified as D-galactose for the B antigen. These sugars can be built on the H antigen, and in cases of the unmodified H antigen, the blood group will be O since the A and B antigens are unable to adhere to the surface of red blood cells [7]. The Rhesus blood group system is composed of Rhesus monkey erythrocyte antigens like the D antigen that can be found on the red cells of most Rh+ humans. This system is highly complicated, and some Rh alloantigens have yet to be biochemically described [8]. Because blood types are unaffected by environmental factors, they are a useful and essential resource in the pathogenesis of diseases. In this regard, many investigations have been conducted to study the relationship between cancer types, blood types, and other disorders [9].

Objectives

Also, some case series demonstrated substantial connections between blood groups and autoimmune disorders like multiple sclerosis, psoriasis, and pemphigus [10-12]. However, the exact nature of the linkage between blood groups and AA is not identified. Thus, we investigated the association between AA and ABO, and Rh systems.

Methods

The current cross-sectional study investigated the association between AA and ABO/Rh blood groups. The study was conducted on 200 cases with AA and 200 healthy controls (HCs) that attended our dermatology clinic in Hospitals between March 2021 and September 2021. Participants with other autoimmune and systemic disorders were excluded. The patients referred to the AA clinic were enrolled in the study and our healthy control objects were selected among people who did not have known systemic and skin disorders and were often referred for cosmetic problems. We matched age and sex between the two groups.

We followed the principles of the Helsinki Declaration. The Institutional Review Board of our university approved the protocol of this study. Informed consent was attained from all participants.

Statistical Analysis

SPSS version 20 (IBM Company, USA) was applied to analyze the variables. Continuous variables are displayed as mean (standard deviation), and categorical variables are reported as frequency (percentage). Student T-test (two-tailed) was applied for the comparison of continuous variables. The Chi-square or Fisher’s exact test was employed for the comparison of the categorical variables between the two study groups. A P-value <0.05 was regarded as significant.

Results

Baseline Characteristics of Participants

Two hundred patients with AA and 200 HCs were included. The baseline characteristics of the subjects in the AA and HC groups are detailed in Table 1. The two study groups were comparable in terms of age, sex, and BMI.

Of 200 AA patients, 81 patients had patchy hair loss, 80 had Universalis hair loss, 35 had Totalis hair loss, and 3 had Ophiasis hair loss. Nail involvement was seen in 51 patients to some degree and in 19 patients as dystrophy (Table 1).

Comparison of Blood Groups Between AA Patients and HCs

Table 2 indicates the frequency of different types of blood groups in AA patients and HCs. ABO blood groups were significantly different between study groups (p=0.001). In this regard, the AA group showed a higher prevalence of the AB blood group, while the prevalence of the O, A, and B blood groups was higher in HCs (p=0.001). Nonetheless, no significant between-group differences were found based on O/non-O (p=0.391) and Rh (p=0.605) blood groups. Finally, ABO*Rh blood groups were significantly different between study groups (p=0.017). The most difference was related to the AB+ blood group, whose frequency was markedly higher in patients with AA compared to HCs (Table 2).

Association Between Blood Groups and Clinical Characteristics in Patients with AA

According to Table 3, no significant association was detected between sex, BMI, disease duration, age of onset, SALT
Table 1. Baseline characteristics of the patients in AA and HC groups.

<table>
<thead>
<tr>
<th></th>
<th>AA group (n=200)</th>
<th>HC group (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years; mean (SD)]</td>
<td>33.26 (14.33)</td>
<td>33.73 (12.05)</td>
<td>0.726*</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>77 (38.5%)</td>
<td>70 (35%)</td>
<td>0.468*</td>
</tr>
<tr>
<td>• Female</td>
<td>123 (61.5%)</td>
<td>130 (65%)</td>
<td></td>
</tr>
<tr>
<td>BMI [kg/m²; mean (SD)]</td>
<td>25.87 (17.86)</td>
<td>26.06 (23.11)</td>
<td>0.926*</td>
</tr>
<tr>
<td>Disease duration [years; mean (SD)]</td>
<td>8.56 (8.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset [years; mean (SD)]</td>
<td>23.15 (12.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current episode [months; mean (SD)]</td>
<td>8.25 (7.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SALT score [mean (SD)]</td>
<td>75.68 (29.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The pattern of hair loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patchy</td>
<td>81 (40.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Universalis</td>
<td>80 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Totalis</td>
<td>35 (17.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ophiasis</td>
<td>3 (1.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• None</td>
<td>129 (64.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Some</td>
<td>51 (25.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dystrophy</td>
<td>19 (9.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A P-value of < 0.05 was considered statistically significant.
SD: standard deviation
* Student T-test
b Chi-square test

Table 2. Comparison of different types of blood groups between AA and Healthy control group groups.

<table>
<thead>
<tr>
<th></th>
<th>AA group (n=200)</th>
<th>HC group (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO [n (%)]</td>
<td></td>
<td></td>
<td>0.001a</td>
</tr>
<tr>
<td>• O</td>
<td>60 (30%)</td>
<td>68 (34%)</td>
<td></td>
</tr>
<tr>
<td>• A</td>
<td>61 (30.5%)</td>
<td>79 (39.5%)</td>
<td></td>
</tr>
<tr>
<td>• B</td>
<td>21 (10.5%)</td>
<td>28 (14%)</td>
<td></td>
</tr>
<tr>
<td>• AB</td>
<td>58 (29%)</td>
<td>25 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Rh [n (%)]</td>
<td></td>
<td></td>
<td>0.605*</td>
</tr>
<tr>
<td>• Negative</td>
<td>17 (8.5%)</td>
<td>20 (10%)</td>
<td></td>
</tr>
<tr>
<td>• Positive</td>
<td>183 (91.5%)</td>
<td>180 (90%)</td>
<td></td>
</tr>
<tr>
<td>ABO*Rh [n (%)]</td>
<td></td>
<td></td>
<td>0.017b</td>
</tr>
<tr>
<td>• O-</td>
<td>9 (4.5%)</td>
<td>10 (5%)</td>
<td></td>
</tr>
<tr>
<td>• A-</td>
<td>3 (1.5%)</td>
<td>5 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>• B-</td>
<td>3 (1.5%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>• AB-</td>
<td>2 (1%)</td>
<td>1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>• O+</td>
<td>51 (25.5%)</td>
<td>58 (29%)</td>
<td></td>
</tr>
<tr>
<td>• A+</td>
<td>58 (29%)</td>
<td>74 (37%)</td>
<td></td>
</tr>
<tr>
<td>• B+</td>
<td>18 (9%)</td>
<td>24 (12%)</td>
<td></td>
</tr>
<tr>
<td>• AB+</td>
<td>36 (28%)</td>
<td>24 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

HC: Healthy control. A P-value of < 0.05 was considered statistically significant.
a Chi-square test
b Fisher exact test
Table 3. Association between blood groups and clinical characteristics of patients with AA.

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>A</th>
<th>B</th>
<th>AB</th>
<th>P-value</th>
<th>Rh -</th>
<th>Rh +</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (36.7%)</td>
<td>30 (49.2%)</td>
<td>7 (33.3%)</td>
<td>18 (31%)</td>
<td>0.201\textsuperscript{a}</td>
<td>9 (52.9%)</td>
<td>115 (62.8%)</td>
<td>0.201\textsuperscript{a}</td>
</tr>
<tr>
<td>Female</td>
<td>38 (63.3%)</td>
<td>31 (50.8%)</td>
<td>14 (66.7%)</td>
<td>40 (69%)</td>
<td></td>
<td>8 (47%)</td>
<td>68 (37.2%)</td>
<td></td>
</tr>
<tr>
<td>BMI [kg/m²; mean (SD)]</td>
<td>24.37 (4.00)</td>
<td>24.39 (4.62)</td>
<td>30.16 (35.47)</td>
<td>28.61 (35.31)</td>
<td>0.687\textsuperscript{a}</td>
<td>25.87 (17.86)</td>
<td>26.06 (23.11)</td>
<td>0.926\textsuperscript{a}</td>
</tr>
<tr>
<td>Disease duration [years; mean (SD)]</td>
<td>8.90 (8.68)</td>
<td>7.81 (7.55)</td>
<td>7.48 (8.02)</td>
<td>9.71 (7.93)</td>
<td>0.290\textsuperscript{a}</td>
<td>8.83 (8.17)</td>
<td>6.75 (6.44)</td>
<td>0.310\textsuperscript{a}</td>
</tr>
<tr>
<td>Age of onset [years; mean (SD)]</td>
<td>23.81 (11.61)</td>
<td>20.67 (11.30)</td>
<td>19.76 (9.43)</td>
<td>26.31 (16.06)</td>
<td>0.175\textsuperscript{a}</td>
<td>23.03 (13.11)</td>
<td>24.41 (11.14)</td>
<td>0.667\textsuperscript{a}</td>
</tr>
<tr>
<td>SALT score [mean (SD)]</td>
<td>71.80 (31.40)</td>
<td>77.44 (29.64)</td>
<td>82.66 (25.92)</td>
<td>75.31 (30.15)</td>
<td>0.508\textsuperscript{a}</td>
<td>75.51 (30.71)</td>
<td>77.41 (28.06)</td>
<td>0.804\textsuperscript{a}</td>
</tr>
<tr>
<td>Hair loss [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.544\textsuperscript{a}</td>
<td></td>
<td></td>
<td>0.060\textsuperscript{a}</td>
</tr>
<tr>
<td>Patchy</td>
<td>28 (46.7%)</td>
<td>20 (33.3%)</td>
<td>8 (38.1%)</td>
<td>25 (43.1%)</td>
<td></td>
<td>7 (41.2%)</td>
<td>74 (40.7%)</td>
<td></td>
</tr>
<tr>
<td>Universalis</td>
<td>22 (36.7%)</td>
<td>29 (48.3%)</td>
<td>10 (47.6%)</td>
<td>19 (32.8%)</td>
<td></td>
<td>9 (52.9%)</td>
<td>71 (39%)</td>
<td></td>
</tr>
<tr>
<td>Totalis</td>
<td>9 (15%)</td>
<td>9 (15%)</td>
<td>3 (14.3%)</td>
<td>14 (24.1%)</td>
<td></td>
<td>0 (0%)</td>
<td>35 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>Ophiasis</td>
<td>1 (1.7%)</td>
<td>2 (3.3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
<td>1 (5.9%)</td>
<td>2 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Nail involvement [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.090\textsuperscript{a}</td>
<td></td>
<td></td>
<td>0.457\textsuperscript{a}</td>
</tr>
<tr>
<td>None</td>
<td>39 (66.1%)</td>
<td>43 (70.5%)</td>
<td>16 (76.2%)</td>
<td>31 (53.4%)</td>
<td></td>
<td>13 (76.5%)</td>
<td>116 (63.7%)</td>
<td></td>
</tr>
<tr>
<td>Some</td>
<td>15 (25.4%)</td>
<td>15 (24.6%)</td>
<td>5 (23.8%)</td>
<td>16 (27.6%)</td>
<td></td>
<td>4 (23.5%)</td>
<td>47 (25.8%)</td>
<td></td>
</tr>
<tr>
<td>Dystrophy</td>
<td>5 (8.5%)</td>
<td>3 (4.9%)</td>
<td>0 (0%)</td>
<td>11 (19%)</td>
<td></td>
<td>0 (0%)</td>
<td>19 (10.4%)</td>
<td></td>
</tr>
</tbody>
</table>

P-value of < 0.05 was considered statistically significant. an Independent t-test
score, patterns of hair loss, nail involvement, and ABO/Rh blood groups in patients with AA (p>0.05).

Discussion

We assessed the relationship between AA and ABO and Rh blood groups. The prevalence of blood groups O, A, B, and AB in patients with AA was 30%, 30.5%, 10.5%, and 29%, respectively. A significant difference was detected between the two study groups regarding the frequency of the ABO blood group. The highest difference was related to the AB blood group, so compared to HCs, patients with AA showed a higher frequency of the AB blood group. The highest difference was related to the AB+ blood group, so compared to HCs, patients with AA showed a higher frequency of the AB+ blood group.

AA is a recurrent inflammatory disorder that affects people of all ages and genders. Despite the disease’s importance, the specific etiology has yet to be fully understood. The ABO blood group family antigens have long been identified. Blood group alloantigens can be found on the membrane of epithelial cells and red blood cells. There is a link between blood types and various dermatologic conditions [9, 13, 14], leading to the elucidation of disease pathogenesis. For instance, malignant melanoma was found to have a statistically significant higher risk in patients with the O blood group [9]. Several previous reports have linked certain infections to specific ABO blood groups [15]. Tuberculoid leprosy is linked to the O blood group, while lepromatous leprosy is linked to the A and B blood groups, gonorrhea to the B blood group, smallpox to the A and B blood groups, and Escherichia coli O 157 infection to the O blood type [16]. Many studies have investigated the association between blood groups and autoimmune disorders like pemphigus Vulgaris, DM, RA, spondyloarthropathy, vasculitis, Behcet’s disease, SLE, systemic sclerosis, and Sjogren’s syndrome [10,17, 18]. Among these, no link was found between the ABO blood types and pemphigus Vulgaris, which is a well-known autoimmune skin disorder [18, 19]. In the etiopathogenesis of AA, autointimmunity is more prominent. Different researchers have established the relevance of T cells in the disease [20]. However, genetic variables play a role in illness susceptibility and severity as well. In single-twin investigations, the frequency of concurrent disease was found to be 55 percent, indicating that genetic and environmental variables play a role in the disease’s development [20, 21]. The genes that code for blood group antigens are found on chromosome 9q34.2 (for the ABO blood group) and chromosome 1p36.11 (for the Rh blood group) [22].

Up to now, only two investigations have examined the relationship between blood type and AA. In 2018, İslamoglu et al. [23] conducted a clinical study in Turkey to investigate the association between alopecia areata and ABO and Rh blood groups. They indicated a similar distribution of the ABO blood group in the patient and healthy groups. However, the Rh+ blood group was markedly higher in the healthy group than the patient group. Also, Rather et al. [24] conducted a case-control study in Kashmir to examine the relationship between ABO blood groups and different skin diseases (psoriasis, vitiligo, AA, pemphigus Vulgaris). Also, 37.1% of patients with psoriasis showed O blood group, followed by type B (30%) and A (25.7%), with no significant differences between study groups. In cases with vitiligo, 47.4% showed the B blood group, followed by blood groups O (36.8%) and A (10.5%). The frequency of A and B blood groups was significantly different between vitiligo patients and controls. In AA patients, blood group B was detected in 45.2% of patients, and groups O (28.6%) and A (19%) ranked second and third, with no significant differences between study groups. In patients with pemphigus Vulgaris, 40% of patients showed O and B blood groups, followed by blood group A (20%), with no significant differences between the groups. Contrary to the results of these studies, a significant difference was found between the two groups in our study. The highest difference was related to the AB+ blood group, so compared to the control group, patients with AA belonged to the AB blood group with higher frequency. We also examined the relationship between the characteristics of AA and the frequency of ABO and Rh blood groups; no significant association was detected between ABO or Rh blood groups and sex, BMI, disease duration, age of onset, SALT score, hair loss pattern, and nail involvement in patients with AA.

Conclusion

A significant difference was found between the two groups regarding the frequency of the ABO+Rh blood group. The frequency of the AB+ blood group was higher in patients with AA. Further studies could verify the results of this study.

References


Dermoscopic Findings in Intraepidermal Carcinoma: an Interobserver Agreement Study

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Key words: intraepidermal carcinoma, squamous cell carcinoma in situ, Bowen’s disease, dermoscopy, interobserver agreement


Accepted: January 12, 2023; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: A wide range of descriptive terms have been used for dermoscopic findings in intraepidermal carcinoma (IEC) and the clinical diagnostic accuracy of IEC can be challenging. Furthermore, dermoscopic findings in IEC have only rarely been evaluated in fair-skinned populations.

Objectives: To measure the interobserver agreement between dermatologists for dermoscopic findings in IEC. Furthermore, to describe the frequency of these findings in a predominantly fair-skinned population.

Methods: One hundred dermoscopic images of histopathologically verified IECs were collected. The 11 most common dermoscopic findings described in previous studies were re-defined in a new terminology in a pre-study consensus meeting. Images were assessed by eight experienced international dermatoscopists. The frequency of findings and the interobserver agreement was analyzed.
Introduction

Intraepidermal carcinoma (IEC), also known as Bowen’s disease or cutaneous squamous cell carcinoma in situ, manifests clinically as a slow-growing, pinkish to brown plaque with scale and/or erosions, often occurring on chronically sun-exposed skin in the elderly. Histopathologically, IEC is characterized by atypical keratinocytes restricted to but spanning the full thickness of the epidermis [1].

Numerous dermoscopic findings in IEC have been described, including the presence of glomerular or dotted vessels, scales, erosions, erythema, white structureless areas, brown structureless pigmentation and brown dots in linear alignment [2-12]. Nevertheless, clinical diagnostic accuracy has been shown to be low in a previous study from our group [3], and several differential diagnoses, both benign and malignant, have been described to have similar dermoscopic findings [8, 12]. This may lead to unnecessary biopsies or inappropriate management. There is also a lack of studies exploring the interobserver agreement on the dermoscopic findings of IEC. Furthermore, dermoscopic findings in IEC have mainly been described in Southern European [3, 8-10], Asian [2, 4, 5] and Middle Eastern populations [7], and only rarely in predominantly fair-skinned populations [11, 12]. To be useful in a clinical setting and for teaching dermoscopy, a high level of interobserver agreement on dermoscopic findings in IEC is advisable. Knowledge regarding the level of interobserver agreement can also be used to refine the core teaching methods to identify IEC. Finally, evaluation of the prevalence of pigmented and non-pigmented dermoscopic structures in IEC in fair-skinned populations would be valuable in a clinical setting.

Objectives

In this study, we aimed to measure the interobserver agreement between dermatologists for identification of predefined dermoscopic findings in IEC. Furthermore, we aimed to describe the presence of these findings in a predominantly fair-skinned population, and possibly identify new diagnostic criteria to help identify IEC.

Methods

This retrospective, cross-sectional study of dermoscopic findings in IEC was performed at Sahlgrenska University Hospital in Gothenburg, Sweden, between September 1, 2020 and November 30, 2021. Dermoscopic image data were collected from a separate study cohort focusing on treatment of IEC. This cohort mainly consisted of patients with predominantly skin types I-III, although skin type was not consistently reported. One hundred dermoscopic images of histopathologically verified IECs were collected prospectively and consecutively from this study cohort. Dermoscopic images were taken with an iPhone 8 (Apple, Cupertino, California, USA) using a Dermlite DL4 deroscope (DermLite LLC, Capistrano, California, USA) in polarizing mode. Unfocused images and images not showing the entire lesion were excluded. All dermoscopic images as presented to the dermatologists (readers) are made available in the supplementary material (Appendix S1). The study was approved by the Regional ethical review board in Gothenburg (approval number 283-18).

Based on the results from previous publications on the dermoscopic findings of IEC [2-6, 9, 10], the 11 most commonly described findings were selected and re-defined in a pre-study consensus meeting (Table 1). Eight readers from Sweden, Italy, Greece, United Kingdom, U.S.A., Argentina, Japan and Australia were invited to participate in the consensus meeting and subsequent image analysis. All readers had >10 years of experience of dermoscopy use. During the consensus meeting, 20 dermoscopic images of IEC (not included in the study dataset) were assessed and discussed until consensus was reached regarding the final list of dermoscopic findings and their definitions (Table 2). The previously described findings of “erosions”, “ulceration” and/or “blood spots” were grouped and named “hemorrhage”. “Erythema”, “white structureless areas” and “hypopigmented (pink, skin-colored or white) structureless areas” were also clustered into the term “pinkish-white areas”. “Shiny white structures” were divided into stromal (shiny white lines, blotches and/or strands) and follicular (rosettes

Results: Scales (83%), dotted/glomerular vessels (77%), pinkish-white areas (73%) and hemorrhage (46%) were the most commonly present dermoscopic findings. Pigmented structures were found in 32% and shiny white structures (follicular or stromal) in 34% of the IEC. Vascular structures (vessels and/or hemorrhage) could be seen in 89% of the lesions. Overall, the interobserver agreement for the respective dermoscopic findings was poor to moderate, with the highest kappa values noted for scales (0.55) and hemorrhage (0.54) and the lowest for pinkish-white areas (0.015).

Conclusion: Our results confirm those of previous studies on dermoscopy in IEC, including the frequency of pigmented structures despite the fair-skinned population. The interobserver agreement was relatively low. The proposed new terminology and our findings can hopefully serve as a guideline for researchers, teachers and students on how to identify IEC.
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</tr>
</thead>
<tbody>
<tr>
<td>Vascular structures</td>
<td>Glomerular vessels</td>
<td>Dotted 60.7%, glomerular 60.7%</td>
<td>Glomerular 69.2%</td>
<td>Glomerular 94%, dotted 64%</td>
<td>Coiled 79.4%, dotted 20.6%</td>
<td>Glomerular 77%, dotted 12%</td>
<td>Glomerular 90%</td>
<td>Coiled vessels 44.2%, vessels arranged in clusters 5.8%</td>
<td>Glomerular 60%, red globules 32%, red globular rings 2%, red dots 60%</td>
</tr>
<tr>
<td></td>
<td>Hairpin vessels</td>
<td>Hairpin (tortuous/looped vessels) 15.7%</td>
<td>Hairpin 42%</td>
<td>Looped 14.7%</td>
<td></td>
<td></td>
<td></td>
<td>Hairpin 36%</td>
<td></td>
</tr>
<tr>
<td>Linear vessels</td>
<td>Short fine telangiectasia 31.5%, arborizing 11.1%</td>
<td>Linear irregular 42.5%</td>
<td>Straight 2.9%, curved 2.9%, serpentine 11.8%, helical 2.9%</td>
<td>Linear irregular 12%, polymorphous/ atypical 8%</td>
<td>Vessels arranged in linear fashion 11.5%,</td>
<td></td>
<td></td>
<td>Arbonizing 6%, atypical red 54%, comma 22%, corkscrew 10%</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Erosions 34.8%, large ulcerations/ bleeding 38.2%</td>
<td>Ulceration 15.1%, focal hemorrhages 55.5%</td>
<td>Ulcer 6%</td>
<td>Erosions 17.6%, ulcerations 26.5%, blood spots 32.4%</td>
<td>Ulceration 19%</td>
<td>Ulceration 28.6%</td>
<td>Hemorrhage, ulceration 44%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratin-related structures</td>
<td>Scales (white or yellow)</td>
<td>White 56.2%, yellow 41.6%</td>
<td>Scleral surface 78.8%, yellow crusts 56.8%, cotton candy sign 6.8%</td>
<td>Scaling 94%</td>
<td>Scales 98%</td>
<td>Scales 90%</td>
<td>Hyperkeratosis 48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keratin rim</td>
<td>Double-edge sign 30.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pigmented structures</td>
<td>Structureless brown pigmentation</td>
<td>Clusters of brown structureless areas 38.4%, homogenous pigmentation 34.9%</td>
<td>Structureless pigmentation 33%</td>
<td>Brown structureless pigmentation 29.4%</td>
<td>Structureless (homogenous) pigmentation 27%</td>
<td>Structureless (homogenous) pigmentation 80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown-gray dots</td>
<td>Brown dots arranged in peripheral lines 9.0%, brown dots scattered 28.1%, blue-gray dots/globules 1.1%</td>
<td>Gray granules 39.7%, peripheral radial streaks 34.9%, brown dots/globules 28.8%</td>
<td>Pigment streaks 6%, pigment network 4%, gray dots/globules 23%</td>
<td>Brown dots 5.9%, linear arranged dots 5.9%</td>
<td>Brown globules 31%, black globules 11.5%</td>
<td>Brown globules 90%</td>
<td>Brown or gray dots arranged in a linear fashion 21.2%</td>
<td>Blue-gray ovoid nests 6%, brown dots/globules 4%, negative pigment network 8%</td>
<td></td>
</tr>
<tr>
<td>Pinkish-white areas</td>
<td>pseudonetwork 9.6%</td>
<td>Pinkish-white network 77%</td>
<td>Erythema 85.3%, white structureless 20.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiny white structures</td>
<td>Stromal structures</td>
<td>Focal/multifocal hypopigmentation 44.5%</td>
<td>White clods 11.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular structures</td>
<td>White shiny blotches and strands 9.0%</td>
<td></td>
<td>White circles 14.7%, four-dot-clods 14.7%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table 2. Definitions of the dermoscopic findings.

<table>
<thead>
<tr>
<th>Dermoscopic category</th>
<th>Pre-defined dermoscopic finding</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular structures</td>
<td>Glomerular vessels</td>
<td>Dotted/glomerular/coiled vessels (clustered, linear or diffuse)</td>
</tr>
<tr>
<td></td>
<td>Hairpin vessels</td>
<td>Hairpin/looped vessels</td>
</tr>
<tr>
<td></td>
<td>Linear vessels</td>
<td>Thin linear and/or branched vessels</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>Erosions, ulceration and/or blood spots</td>
</tr>
<tr>
<td>Keratin-related structures</td>
<td>Scales</td>
<td>White and/or yellow scales</td>
</tr>
<tr>
<td></td>
<td>Keratin rim</td>
<td>Peripheral rim of keratin as would be expected in typical cases of porokeratosis; no other peripheral scaling</td>
</tr>
<tr>
<td>Pigmented structures</td>
<td>Pinkish-white areas</td>
<td>Pinkish and/or white areas</td>
</tr>
<tr>
<td></td>
<td>Brown pigmented areas</td>
<td>Areas with brown pigmentation</td>
</tr>
<tr>
<td></td>
<td>Brown-gray dots</td>
<td>Brown or gray dots or globules</td>
</tr>
<tr>
<td>Shiny white structures</td>
<td>Stromal structures</td>
<td>Shiny white lines, blotches and/or strands</td>
</tr>
<tr>
<td>Follicular structures</td>
<td>Rosettes or white circles</td>
<td></td>
</tr>
</tbody>
</table>

or white circles) structures. All dermoscopic findings were noted as present regardless of size, number, and distribution with the exception of the item “keratin rim” which inherently is distributed at the border of the lesion. Each dermoscopic finding was marked as present or absent. If further unlisted but relevant dermoscopic findings were identified, the readers were requested to specify these separately. The anonymized outcome from each reader is available as supplementary material (Appendix S2).

Statistics
The interobserver agreement for each dermoscopic finding was calculated using Fleiss’ Kappa. The resulting Kappa values were interpreted as: poor (≤0), slight (>0 to 0.20), fair (>0.2 to 0.4), moderate (>0.4 to 0.6), substantial (>0.6 to 0.8) or almost perfect (>0.8) agreement. In addition, Fisher’s exact test was used to compare the frequency distribution of the dermoscopic findings. All data were analyzed using R version 3.5.3.

Results
Images of 100 IECs in 94 patients (43 females [46%]) were included. The median age of the patients was 73 years (range 52-87 years). The most common tumor location was the head and neck area (43%) followed by the trunk (17%), upper limbs (24%) and lower limbs (16%). The median surface diameter of the lesion was 13 mm (range: 5–30 mm).

The frequencies of the dermoscopic findings and the interobserver agreements are summarized in Table 3 and examples are demonstrated in Figure 1. No new dermoscopic findings were described by any of the readers. The most commonly present dermoscopic findings were scales (83%), dotted/glomerular vessels (77%) and pinkish-white areas (73%). Among these, there was moderate agreement between readers for scales (κ=0.55), fair agreement for dotted/glomerular vessels (κ=0.32), but poor to slight agreement for pinkish-white areas (κ=0.02). Hemorrhage was present in almost half of the cases, showing a moderate interobserver agreement. Hairpin vessels and linear vessels were less frequently observed and demonstrated slight to fair interobserver agreement. Keratin rim was the least common finding, but showed a moderate interobserver agreement. Overall, pigmented structures, were shown in 32% of the cases, represented by brown pigmentation (19%) and brown-gray dots (26%) with fair interobserver agreement. Stromal shiny white structures were almost twice as common as follicular ones, and both demonstrated fair interobserver agreement. Shiny white structures overall were present in over half of the lesions (53%) with a fair to moderate agreement (κ=0.40). In 97% of all lesions, either glomerular/dotted vessels, scales or hemorrhage were present (κ=0.41). Furthermore, almost all lesions (89%) showed vascular structures (vessels and/or hemorrhage) (κ=0.22). Figure 2 demonstrates the variation between readers for each dermoscopic finding.

Conclusions
In this retrospective, cross-sectional study of 100 dermoscopic images of IEC, we showed that scales, dotted/glomerular vessels, pinkish-white areas and hemorrhage were the most commonly present dermoscopic findings. Vascular structures could be seen in a majority of the lesions. Overall, the interobserver agreement for the respective dermoscopic findings was slight to moderate, with the highest kappa values noted for scales and hemorrhage.

Characteristic findings, generally regarded as predictive of IEC (scales, dotted/glomerular vessels, and hemorrhage)
Table 3. The frequencies of the dermoscopic findings in IEC and the interobserver agreement between the eight readers.

<table>
<thead>
<tr>
<th>Dermoscopic finding</th>
<th>Frequency, % (95% CI)</th>
<th>Fleiss’ kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular structures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dotted/glomerular vessels</td>
<td>77.1 (74.1-79.9)</td>
<td>0.32 (0.29-0.36)</td>
</tr>
<tr>
<td>Hairpin vessels</td>
<td>26.4 (23.4-29.5)</td>
<td>0.14 (0.11-0.18)</td>
</tr>
<tr>
<td>Linear vessels</td>
<td>30.6 (27.5-33.9)</td>
<td>0.25 (0.22-0.29)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>45.5 (42.1-49.0)</td>
<td>0.54 (0.50-0.57)</td>
</tr>
<tr>
<td><strong>Keratin-related structures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scales</td>
<td>83.3 (80.5-85.7)</td>
<td>0.55 (0.52-0.59)</td>
</tr>
<tr>
<td>Keratin rim</td>
<td>3.4 (2.3-4.9)</td>
<td>0.44 (0.40-0.47)</td>
</tr>
<tr>
<td><strong>Pigmented structures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown pigmentation</td>
<td>25.8 (22.8-28.9)</td>
<td>0.37 (0.34-0.41)</td>
</tr>
<tr>
<td>Brown-gray dots</td>
<td>19.1 (16.5-22.0)</td>
<td>0.30 (0.27-0.34)</td>
</tr>
<tr>
<td>Pinkish-white areas</td>
<td>72.6 (69.4-75.6)</td>
<td>0.02 (-0.02-0.05)</td>
</tr>
<tr>
<td><strong>Shiny white structures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stromal structures</td>
<td>42.8 (39.4-46.2)</td>
<td>0.39 (0.35-0.42)</td>
</tr>
<tr>
<td><strong>Follicular structures</strong></td>
<td>23.5 (20.7-26.6)</td>
<td>0.33 (0.30-0.37)</td>
</tr>
</tbody>
</table>

Figure 1. Images showing the 11 pre-defined dermoscopic findings used in the study: A) dotted/glomerular vessels (stars), keratin rim (black arrow); B) hemorrhage (white arrow), stromal structures (black arrowheads), dotted/glomerular vessels (stars), follicular structures (yellow circle); C) brown pigmented area (square), brown-gray dots (yellow arrowheads), pinkish-white area (black circle) and D) hairpin vessels (white circle) and linear vessels (white arrowhead).
were shown to be present at a similar frequency compared to previous studies [2-6, 9-12]. Scales and dotted/glomerular vessels were among the most common findings, present in four out of five lesions, with fair to moderate agreement. Previous studies have shown scales to be present in 48-92% [2-5, 7, 8, 12] and dotted/glomerular vessels to be present in 60-94% [2-7, 12]. Contrarily, Cameron et al. did not evaluate scales and showed a lower proportion of glomerular (coiled) vessels (44%), which may be due to only including pigmented IEC [11] [13].

The third most common dermoscopic finding in our cohort was pinkish-white areas which, however, showed a very low interobserver agreement. Pinkish-white areas have previously been described in a multitude of ways: pinkish-white network (77%) [4], erythema (85%) and white structureless areas (21%) [7]; hypopigmented (pink, skin colored or white) structureless zones (67%) [11]; and milky pink (8%), light pink (62%), dull pink (8%), and light red (22%) colors [12]. Despite having reached consensus over the definition of the dermoscopic finding of pinkish-white areas before the assessments, this finding seems to be difficult to interpret and should be interpreted with caution as a diagnostic marker for IEC. In fact, colors in general have been shown to be difficult to agree upon. Bajaj et al. showed that morphologic characteristics (i.e., structures and patterns), not color, provide the primary diagnostic clue in dermoscopy [14].

The interobserver agreement on pigmented structures was fair and the overall frequency of these findings was
32%. This is similar to previously mentioned studies in which pigmented structures were observed in around 30% of IECs in cohorts from southern Europe, Asia and the Middle East [2-5, 7]. Taking into consideration that the population in our cohort predominantly was from the northern part of Europe with generally lighter skin types (I-III), 32% was higher than expected.

Over half of the lesions showed shiny white structures, either stromal or follicular, with a moderate interobserver agreement. Several previous publications have described such findings alternately as: shiny white blotches and strands, white clods, white circles or four dot clods [3, 7] (9-15%) and focal/multifocal hypopigmentation (45%) [5]. We believe that shiny white structures have the potential to be useful when describing dermoscopic findings in IEC in the future, given the relatively high frequency and moderate interobserver agreement.

Overall, the interobserver agreement for most dermoscopic findings ranged from poor to moderate. No finding had a higher agreement than $\kappa=0.55$ (scales), followed by $\kappa=0.54$ (hemorrhage). Although no other studies have examined the interobserver agreement for dermoscopic findings in IEC, a study on porokeratosis showed Kappa values that ranged from moderate to almost perfect for similar dermoscopic findings. For example, agreement was almost perfect for keratin rim, blood spots or erosions along the keratin rim, dotted or glomerular vessels and shiny white structures in porokeratosis [15]. Nevertheless, this study only included three readers from a single center, which may have contributed to the higher agreement.

Consensus on the dermoscopic terminology is important and intended to serve as a guideline for students, teachers, and researchers. Recently, the International Dermoscopy Society published a consensus agreement on descriptive and metaphoric terms for dermoscopic findings creating a helpful framework of standardized terms that allow for consistent use of dermoscopic terminology [16]. However, their list of terms did not include all the dermoscopic findings our group identified during our consensus meeting. Furthermore, the terminology used in previous publications on the dermoscopic findings in IEC have varied greatly [2-6, 9-12]. Therefore, we proposed and defined a few new dermoscopic findings (e.g., ‘hemorrhage’ and ‘brown pigmented areas’). We also proposed a new grouping of shiny white structures into ‘stromal’ and ‘follicular’. The keratin-related structures of ‘scales’ and ‘keratin rim’ which have been used to describe porokeratosis [15] were re-used here in an attempt to not introduce more new terms than necessary. Nevertheless, it remains to be shown whether our selected terms and definitions are the most appropriate considering the relatively low interobserver agreement on certain dermoscopic findings.

Strengths of our study include the relatively large number of lesions (n=100) in comparison to previous literature on dermoscopy in IEC, and that all lesions were histopathologically verified. Furthermore, all assessed images and the outcome from each dermoscopic reader are shared in supplementary files, which we believe is important for transparency in dermoscopy research. Although, the international group of readers ensured a diverse assessment, the high number of readers likely decreased the interobserver agreement. Further limitations include the lack of consistent reporting of skin types and the artificial setting without macroscopic images and/or clinical history. Furthermore, we did not include images of other keratinocytic tumors with similar dermoscopic findings. Also, we did not ask the readers to annotate the images to pin-point the exact location of the observed dermoscopic findings.

Confirming previous publications, we found scales, dotted/gglomerular vessels, and hemorrhage to be important dermoscopic findings in IEC with fair to moderate interobserver agreement. Interestingly, brown pigmented structures were more frequent than expected in a predominantly light-skinned population. This study also includes new terminology for dermoscopic findings in IEC, which require further evaluation. Future studies may also benefit from annotation of images to improve our understanding of the interobserver discordance, through directing the focus of the reader to specific areas within the lesion. Our results can hopefully be used to refine and improve the transfer of knowledge to new generations of dermoscopists on how to identify IEC. This could improve clinical diagnosis and enable more efficient lesion management by reducing the number of biopsies needed while still being able to make optimal treatment choices.

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Attitudes Towards Artificial Intelligence Among Dermatologists Working in Saudi Arabia

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Key words: dermatologists, artificial intelligence, attitudes


Accepted: June 17, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Artificial intelligence (AI) and its applications are among the most discussed modern technologies today. Despite the rapidly expanding use of AI in medicine, and specifically in dermatology, only a few studies have studied the attitude of physicians toward AI.

Objective: To recognize the attitudes towards AI among dermatologists in the Kingdom of Saudi Arabia.

Methods: A cross-sectional survey was done among dermatologists in Saudi Arabia. Questionnaires were distributed through several online channels.

Results: Overall, 103 dermatologists filled out the survey. The majority saw very strong or strong potential for AI in the automated detection of skin diseases based on dermatological clinical images (50.9%), dermoscopic images (66.6%) and within dermatopathology (66.6%). In regard to results of attitudes towards AI, 56.6% and 52.8% agreed that AI will revolutionize medicine and dermatology, respectively. However, many of the respondents disagreed that AI will replace physicians (41.5%) and human dermatologists (39.6%) in the future. Age did not impact the overall attitude of dermatologists.

Conclusion: Dermatologists in Saudi Arabia showed an optimistic attitude towards AI in dermatology and medicine. However, dermatologists believe that AI will not replace humans in the future.
Introduction

With the current advancement of technology, algorithms have taken on a huge role in the field of medicine and displaced much of the work of physicians. Artificial intelligence (AI) and its application in various fields are considered one of the most talked about modern technologies today. Experts in medicine have described AI as the stethoscope of the 21st century [1].

AI is a revolution that can help optimize any job. A recent review showed a promising impact on the sensitivity and accuracy in the screening of skin lesions and skin cancer detection [2]. Multiple recent studies demonstrated the benefits of AI. Worldwide, there is an increasing number of impressive attempts at the rapid leveraging of this technology in dermatology [3].

With the rapidly expanding use of AI in medicine and specifically in dermatology, there are only a few studies that discussed the attitude of physicians towards AI. In order to understand the attitudes, an online survey was prepared.

Objective

The goal of the current study is to understand the attitudes towards AI among dermatologists in the Kingdom of Saudi Arabia. To our knowledge, this topic has never been investigated through research in Saudi Arabia.

Materials and Methods

A cross-sectional survey was prepared. Survey forms were disseminated electronically through the Saudi Society of Dermatology and Dermatologic Surgery mailing group and a Saudi dermatologists’ WhatsApp group during the months of September 2020, March and July 2021. Included in the study were dermatologists (consultants and specialists) working or having worked in Saudi Arabia at the time of the survey and who had online access.

The survey was adapted from the form used in an original study by two of the authors [4]. It contained 30 questions including socio-demographic data (gender, age, main practice setting, and years of working in Saudi Arabia), their background knowledge and sources of AI and, lastly, their feelings and attitudes towards AI in dermatology.

Analysis and data management were done using IBM SPSS software version 23 (IBM Corp., Armonk, N.Y., US). Results were presented as counts and percentages for categorical variables while numerical variables were presented by mean and standard deviations. Also, the General Linear Regression Model (GLRM) was used to determine the relation of sex and group with attitudes using scores for the answers. *P*-values <0.05 were considered statistically significant.

Results

Among the 103 dermatologists who responded to the survey, 87 (84.5%) were practicing dermatology in Saudi Arabia and 9 (9.4%) were not, at the time of the study (Table 1). The majority of the respondents were male (n=33, 67.3%), mostly between the ages of 31 to 40 years old (n=17, 34.7%) and had 6-10 years (n=14, 28.6%) experience in dermatology. In regards to their main practice setting, most of the

| Table 1. Socio-demographic characteristics of respondents in the study (n = 103). |
|---|---|---|
| Variables | n | Percentage(%) |
| Practicing in Saudi Arabia | | |
| Yes | 87 | 84.5 |
| No | 9 | 8.7 |
| Skipped | 7 | 6.7 |
| Distribution of answers to the questions below: | | |
| Answered | 49 | 47.6 |
| Skipped | 54 | 52.4 |
| Gender | | |
| Female | 16 | 32.6 |
| Male | 33 | 67.4 |
| Age | | |
| 21-30 years | 2 | 4.1 |
| 31-40 years | 17 | 34.7 |
| 41-50 years | 7 | 14.3 |
| 51-60 years | 8 | 16.3 |
| 61-70 years | 15 | 30.6 |
| Main practice setting | | |
| University hospital | 12 | 24.5 |
| Military hospital | 5 | 10.2 |
| Public teaching hospital | 8 | 16.3 |
| Public non-teaching hospital | 8 | 16.3 |
| Private clinic | 10 | 20.4 |
| Private hospital | 4 | 8.2 |
| Other | 2 | 4.1 |
| Years of working in dermatology | | |
| 0-5 years | 5 | 10.2 |
| 6-10 years | 14 | 28.6 |
| 11-15 years | 6 | 12.2 |
| 16-20 years | 4 | 8.2 |
| 21-25 years | 8 | 16.3 |
| 26-30 years | 2 | 4.1 |
| 31-35 years | 5 | 10.2 |
| 36-40 years | 4 | 8.2 |
| 40 above years | 1 | 2 |
respondents practiced in University hospitals (n=12, 24.5%) followed by private clinics (n=10, 20.4%), public teaching hospitals (n=8, 16.3%) and public non-teaching hospitals (n=8, 16.3%).

Answers regarding background knowledge in AI revealed that 46 (63.9%) knew about AI as a topic in dermatology. However, 11.1% (n=8) had excellent knowledge when it comes to AI in dermatology and the majority (n=20, 27.8%) had only heard about it but not more (Table 2). Meanwhile, when asked about their source of AI information, 68.8%, 65.6%, 42.2%, and 32.8% heard about AI from social media, media, friends, and lectures, respectively (Table 3).

In regard to potential applications of AI in dermatology, respondents believed that AI has a strong potential in the automated detection of skin diseases based on clinical dermatological images (n=20, 35.1%), on dermatoscopic images (n=28, 49.1%) and on dermatopathology images (n=23, 40.4%) (Table 4).

More than half of the respondents considered themselves as well-educated regarding the use of modern technology (n=28, 52.8%). The majority of respondents had read medical publications regarding AI within dermatology (n=25, 51%) while most had not used AI as a diagnostic aid in real life (n=34, 69.4%) (Table 5).

Results of attitudes towards AI revealed that age did not affect the attitudes of dermatologists toward AI overall. In general, 56.6% (n=30) and 52.8% (n=28) agreed that AI will generally revolutionize medicine and dermatology, respectively. Twenty-six (49.1%) agreed that dermatology and medicine become more exciting to them with the increased use of AI. More than half agreed that AI will improve dermatology (n=30, 56.6%) and medicine in general (n=27, 50.9%) and almost half (n=24, 45.3%) agreed that AI must be part of medical training. However, most respondents expressed disagreement regarding AI replacing physicians.

### Table 2. Distribution of answers regarding background knowledge of artificial intelligence.

<table>
<thead>
<tr>
<th>Count</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI is a topic that has become of interest to the Dermatology community.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
</tr>
<tr>
<td>Were you already aware of this topic in Dermatology?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>46</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
</tr>
<tr>
<td>Which degree of knowledge would you say you have when it comes to AI within Dermatology?</td>
<td></td>
</tr>
<tr>
<td>Excellent Knowledge</td>
<td>8</td>
</tr>
<tr>
<td>Good Knowledge</td>
<td>14</td>
</tr>
<tr>
<td>Basic Knowledge</td>
<td>19</td>
</tr>
<tr>
<td>I have heard about it, but not more</td>
<td>20</td>
</tr>
<tr>
<td>I have never heard about it</td>
<td>11</td>
</tr>
</tbody>
</table>

*72 (69.9.%) participants answered this part

### Table 3. Distribution of answers regarding sources of knowledge on artificial intelligence.

<table>
<thead>
<tr>
<th>Sources</th>
<th>Count</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42</td>
<td>65.6</td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>34.4</td>
</tr>
<tr>
<td>Social Media</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44</td>
<td>68.7</td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>31.2</td>
</tr>
<tr>
<td>Lectures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>32.8</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>67.2</td>
</tr>
<tr>
<td>Friends</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>42.2</td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>57.8</td>
</tr>
</tbody>
</table>

*64 (62.1%) participants answered this part

### Table 4. Distribution of answers regarding the potential of artificial intelligence in dermatology*.

<table>
<thead>
<tr>
<th>Question Choices</th>
<th>Very strong potential</th>
<th>Strong potential</th>
<th>Moderate potential</th>
<th>Low potential</th>
<th>No potential</th>
<th>I don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated detection of skin diseases based on dermatological clinical images?</td>
<td>9 (15.8%)</td>
<td>20 (35.1%)</td>
<td>16 (28.1%)</td>
<td>10 (17.5%)</td>
<td>1 (1.7%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Automated detection of skin diseases based on dermatoscopic images?</td>
<td>10 (17.5%)</td>
<td>28 (49.1%)</td>
<td>13 (22.8%)</td>
<td>5 (8.8%)</td>
<td>0 (0%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Automated detection of skin diseases based on dermatopathology images?</td>
<td>15 (26.3%)</td>
<td>23 (40.3%)</td>
<td>11 (19.3%)</td>
<td>6 (10.5%)</td>
<td>0 (0%)</td>
<td>2 (3.5%)</td>
</tr>
</tbody>
</table>

*57 (55.3%) participants answered this part
Table 5. Distribution of answers regarding attitudes towards artificial intelligence among dermatologists in Saudi Arabia.

<table>
<thead>
<tr>
<th>Question Choices</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>I don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI will revolutionize Medicine in general.</td>
<td>16(30.2%)</td>
<td>30(56.6%)</td>
<td>4(7.5%)</td>
<td>2(3.8%)</td>
<td>0(0.0%)</td>
<td>1(1.9%)</td>
</tr>
<tr>
<td>AI will revolutionize Dermatology</td>
<td>16(30.2%)</td>
<td>28(52.8%)</td>
<td>4(7.5%)</td>
<td>3(5.7%)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>AI will revolutionize Dermatology more than other medical specialties in general.</td>
<td>6(11.3%)</td>
<td>15(28.3%)</td>
<td>16(30.2%)</td>
<td>10(18.9%)</td>
<td>2(3.8%)</td>
<td>4(7.5%)</td>
</tr>
<tr>
<td>In the foreseeable future, all physicians will be replaced by AI.</td>
<td>2(3.8%)</td>
<td>4(7.5%)</td>
<td>5(9.4%)</td>
<td>22(41.5%)</td>
<td>17(32.1%)</td>
<td>3(5.7%)</td>
</tr>
<tr>
<td>The human dermatologist will be replaced by AI in the foreseeable future.</td>
<td>2(3.8%)</td>
<td>3(5.7%)</td>
<td>5(9.4%)</td>
<td>21(39.6%)</td>
<td>18(34%)</td>
<td>4(7.5%)</td>
</tr>
<tr>
<td>A development with an increased use of AI in Dermatology frightens me.</td>
<td>3(5.7%)</td>
<td>6(11.3%)</td>
<td>9(17%)</td>
<td>23(43.4%)</td>
<td>12(22.6%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>A development with an increased use of AI in Dermatology makes Dermatology more exciting to me.</td>
<td>14(26.4%)</td>
<td>26(49.1%)</td>
<td>12(22.6%)</td>
<td>1(1.9%)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>A development with an increased use of AI makes Medicine in general more exciting to me.</td>
<td>13(24.5%)</td>
<td>26(49.1%)</td>
<td>11(20.7%)</td>
<td>1(1.9%)</td>
<td>2(3.8%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>AI will improve Dermatology.</td>
<td>15(28.3%)</td>
<td>30(56.6%)</td>
<td>5(9.4%)</td>
<td>1(1.9%)</td>
<td>2(3.8%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>AI will improve Medicine in general.</td>
<td>16(30.2%)</td>
<td>27(50.9%)</td>
<td>7(13.2%)</td>
<td>1(1.9%)</td>
<td>1(1.9%)</td>
<td>1(1.9%)</td>
</tr>
<tr>
<td>AI should be part of medical training.</td>
<td>21(39.6%)</td>
<td>24(45.3%)</td>
<td>5(9.4%)</td>
<td>2(3.8%)</td>
<td>0(0.0%)</td>
<td>1(1.9%)</td>
</tr>
</tbody>
</table>

Section 2

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree nor disagree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>I don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>I consider myself well informed about the use of modern technology, especially computers.</td>
<td>13(26.5%)</td>
<td>28(52.8%)</td>
<td>3(6.1%)</td>
<td>5(10.2%)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Would you consider yourself to be someone who enjoys technology?</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you read any medical publications regarding AI within Dermatology?</td>
<td>25(51.1%)</td>
<td>24(49%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you used AI as a diagnostic aid in real life within Dermatology?</td>
<td>15(30.6%)</td>
<td>34(69.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 53 (51.5%) participants answered this part  
** 49 (47.6) participants answered this part

In this cross-sectional study, dermatologists in Saudi Arabia showed a positive attitude towards AI. Most of the respondents had not used AI in diagnosis in real settings but generally agreed that AI will revolutionize dermatology and medicine.

While 63.9% of the respondents were aware of AI as a topic in dermatology, the majority of them had only heard about it (n=20, 27.8%) and only 11.1% had excellent knowledge. Although the awareness of AI among dermatologists was lower compared to the report of Polesie et al. [4], respondents viewed AI as having strong potential in the detection of skin diseases. Dermatologists saw a stronger potential of AI in detection using dermatoscopic images and within dermatopathology than with dermatological clinical images [4].

Discussion

(n=22, 41.5%) and human dermatologists (n=21, 39.6%) in the future. In addition, 43.4% (n=23) were not frightened about the increased use of AI. The majority of respondents were neutral regarding the proposal that “AI will revolutionize dermatology more than other medical specialties” (n=16, 30.2%).

In this cross-sectional study, dermatologists in Saudi Arabia showed a positive attitude towards AI. Most of the respondents had not used AI in diagnosis in real settings but generally agreed that AI will revolutionize dermatology and medicine.

While 63.9% of the respondents were aware of AI as a topic in dermatology, the majority of them had only heard about it (n=20, 27.8%) and only 11.1% had excellent knowledge. Although the awareness of AI among dermatologists was lower compared to the report of Polesie et al. [4], respondents viewed AI as having strong potential in the detection of skin diseases. Dermatologists saw a stronger potential of AI in detection using dermatoscopic images and within dermatopathology than with dermatological clinical images [4].
In our study, although respondents were optimistic about the increased use of AI in the development of dermatology and medicine in general, the majority (n=21, 39.6%) disagreed that AI will replace doctors. Only 3.8% strongly agreed while 5.7% agreed with this hypothesis. This is consistent with other studies about AI. Polesie et al. reported similar results in which only 5.5% of the participants agreed that human doctors will be displaced by AI [4]. Krittanawong also concluded that although AI may become more effective in diagnosis and image recognition, it cannot replace physicians [5]. In a 2017 survey in the United States, the majority of the respondents were worried about computers replacing humans in the future [6]. This was not the case in Korea, in which only 35.4% of the participants agreed that AI will displace physicians in the future [7].

In this study, the relationship between sex and age was determined and examined. The findings revealed that dermatologists’ attitudes toward AI were unaffected by their age. Similar results were found in the study of Polesie et al. [4].

The current study has some limitations. First, since this is a cross-sectional survey, selection bias and social desirability biases are possible. Due to the selected method of distributing the survey, the response rate could not be calculated. Participants may be more optimistic than those who did not participate. Second, not all the questions in the survey were answered by the participants, some were skipped, resulting also in possible selection bias.

Conclusion

Dermatologists in Saudi Arabia showed an overall positive attitude towards AI in dermatology. Overall, age did not affect the attitudes of dermatologists about AI. Furthermore, results showed that most dermatologists were aware of the potential of AI in the automated detection of skin diseases using dermatoscopic, histopathological and clinical dermatological images. Moreover, they agreed that AI will revolutionize dermatology and the development of AI within our specialty seemed exciting to them. However, most participants believed that AI will not replace physicians in the future.

References

Infections in Hospitalized Patients with Psoriasis in a Skin Referral Hospital

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2 Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran
3 Department of Infectious Diseases, Tehran University of Medical Sciences, Tehran, Iran

Key words: psoriasis, infection, biologic treatment, anti-TNFα, methotrexate

Citation: Zaredar N, Mhamoudi H, Soori T, et al. Infections In Hospitalized Patients With Psoriasis In A Skin Referral Hospital. Dermatol Pract Concept. 2023;13(1):e2023027. DOI: https://doi.org/10.5826/dpc.1301a27

Accepted: July 15, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Psoriasis and its treatments may predispose patients to various infections. This is considered one of the most significant complications in patients with psoriasis.

Objectives: In the present study, we aimed to determine the prevalence of infection in hospitalized psoriasis patients and its relationship with systemic and biologic treatments.

Methods: All hospitalized patients with psoriasis from 2018 to 2020 in Razi Hospital in Tehran, Iran, were studied and cases of infection were recorded.

Results: Overall, 516 patients were studied and 25 types of infection in 111 patients were found. The most common types of infection were pharyngitis and cellulitis, followed by oral candida, urinary tract infections, common cold, fever of unknown origin, and pneumonia. Female sex and pustular psoriasis were significantly associated with infection in psoriatic patients. Those patients who received prednisolone had a higher risk of infection, and those under treatment with methotrexate or infliximab had a lower risk of infection.

Conclusion: Overall, 21.5% of psoriasis patients in our study had at least one episode of infection. This demonstrates that the prevalence of infection in these patients is not low. Using systemic steroids was associated with a higher risk of infection, while using methotrexate or infliximab was concomitant with a lower risk of infection.
Introduction

Psoriasis is a common, chronic, inflammatory cutaneous disease, causing morbidity and mortality in severe cases. The approximate prevalence rate is 0.14-5.32% of the general population. [1, 2]

The characteristic of psoriasis is sustained inflammation which causes uncontrolled proliferation of keratinocytes and dysfunctional differentiation that activates through TNF-α, IL-17, and IFN-γ.

The psoriatic plaque's histology shows acanthosis, which covers inflammatory infiltrates consisting of dermal dendritic cells, macrophages, T cells, and neutrophils as well as neovascularization [3].

Infections are among the most concerning complications of psoriasis per se and its treatments. Two types of conventional and biological treatments are used to treat this disease. Biologic treatments are mostly used in more severe psoriasis patients; however, infections are the most crucial side effect of these drugs. Recent studies have found conflicting results regarding the prevalence of infection in this disease and its relationship with various systemic treatments. This study evaluated the prevalence of infection in psoriasis hospitalized patients in a skin referral hospital and its relationship with variables such as biologic treatments in hospitalized patients with psoriasis.

Methods

In this retrospective cross-sectional study, all hospitalized psoriasis patients from 2018 to 2020 in Razi Hospital in Tehran, Iran were examined for any documented infection. Demographic data, psoriasis subtypes, the existence of arthropathy, and present treatments (methotrexate, prednisolone, cyclosporine, acitretin, phototherapy, topical treatment, and biological treatment) were extracted. Furthermore, the wound, blood, and urine culture results were recorded. All hospital records over the course of the study were reviewed and cases of diagnosed psoriasis were included in the study. Cases of comorbid psoriasis with other skin disease were excluded.

These data were analyzed with SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Associations between infections and other variables were examined using the Chi-Square test. The frequency has been calculated for quantitative data, mean and standard deviation, for qualitative data. The significance level was considered a P-value < 0.05. Confidence interval (CI) is the range of values between which you expect your estimate to be if you repeat your test, at a certain level of confidence.

An odds ratio (OR) is a measure of how an exposure relates to a result. The OR represents the probability that a result will occur as a result of a particular exposure compared to the probability that the result will occur in the absence of that exposure.

Results

Among 516 patients, 172 (33%) women and 344 (67%) men, with a mean age of 43.85 +/- 15.95 (range: 8 to 89). The mean age of men was greater than women (44.97 +/- 15.40 vs 41.62 +/- 16.83) (P-value: 0.024).

380 (73.6%), 106 (20.5%), 25 (4.8%), 4 (0.8%) and 1(0.2%) were plaque-type, pustular, erythrodermic, inverse and guttate, respectively.

Furthermore, from 248 available data, 144 (58.06%) patients had arthropathy. Meanwhile, 111 (21.5%) patients had at least one episode of infection; overall, 166 cases were detected.

Considering the low number of patients with inverse and guttate psoriasis, only plaque-type, pustular and erythrodermic psoriasis were analyzed.

The most common types of infection were pharyngitis, cellulitis followed by oral candidiasis, urinary tract infections (UTI), common cold, fever of unknown origin (FUO), and pneumonia (Table 1).

There was a significant correlation between age and oral candidiasis, UTI, and herpes simplex virus (HSV) infection (P-values: 0.023, 0.012, 0.001, respectively), while no significant relationship was found between age and other types of infections (P-value<0.05 for all).

Infections were 2 times more frequent in women (30.2%) than men (17.2%) (OR: 2.09, 95%CI: 1.36-3.21, P-value: 0.001). Additionally, oral candidiasis, flexural candidiasis, and erythrasma were significantly more common in women (P-values: 0.011, 0.044, 0.001, respectively).

Regarding psoriasis subtypes, there was a significant relation between plaque-type and pustular psoriasis with infection (P-values: <0.001, OR: 0.282; P-value <0.001, OR: 3.845, respectively). In other words, patients with pustular and plaque-type psoriasis had a 3.8 and 2.8 times higher risk of infection in comparison with other subtypes, respectively. Furthermore, cellulitis, pharyngitis, FUO, oral candidiasis, UTI, vaginal candidiasis, and bacterial blepharitis were significantly more common in the pustular subtype (Table 2).

Concerning the relationship between medications and infection, patients treated with prednisolone (OR: 2.93, 95%CI: 1.82-4.73, P-value< 0.001) had a higher risk of infection. From a total of 99 cases on prednisolone, 38 (38.4%) had at least one episode of infection, while the infection was seen in 73 (17.5%) out of 417 cases who were not receiving prednisolone (P-value: <0.001, OR: 2.93).

On the other hand, those under treatment of methotrexate (OR: 2.1, 95%CI: 0.29-0.76, P-value: 0.002) or infliximab (OR: 5.12, 95%CI: 1.0-10.35, P-value< 0.001) had a lower risk of infection (Table 3).
In patients on prednisolone, the risk of cellulitis, pharyngitis, common cold, FUO, UTI, and blepharitis was higher. Additionally, cyclosporine was associated with a higher risk of FUO and patients receiving methotrexate had a lower chance of pharyngitis (Table 4).

Regarding the anti-TNFα group, infliximab was associated with a lower risk of cellulitis (OR: 0.04, P-value: 0.001) (Table 4), while adalimumab and etanercept were not linked to any type of infection (all p-values>0.05). It is worth noting that although no case of active tuberculosis was recognized,
detected micro-organisms in blood cultures. In urine cultures, E-coli (18.51%) followed by Pseudomonas (11.11%), and in wound cultures, Staph epidermidis (29.76%) followed by Staphylococcus aureus (28.57%) were the most common pathogens.

63 (12.2%) patients received isoniazid due to positive PPD and use of immunosuppressive therapy.

Culture results were available in 82 cases; 45 (54.8%) were negative. Staphylococcus epidermidis (36.36%) followed by Enterobacter (9.09%) were the most commonly detected micro-organisms in blood cultures. In urine cultures, E-coli (18.51%) followed by Pseudomonas (11.11%), and in wound cultures, Staph epidermidis (29.76%) followed by Staphylococcus aureus (28.57%) were the most common pathogens.

### Table 3. The relationship between infections and current treatments.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Total</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>237</td>
<td>83</td>
<td>320</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>74.10%</td>
<td>25.90%</td>
<td>100.00%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Count</td>
<td>168</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>85.70%</td>
<td>14.30%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Count</td>
<td>344</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>82.50%</td>
<td>17.50%</td>
<td>100.00%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Count</td>
<td>61</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>61.60%</td>
<td>38.40%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Count</td>
<td>386</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>78.90%</td>
<td>21.10%</td>
<td>100.00%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Count</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>70.40%</td>
<td>29.60%</td>
<td>100.00%</td>
</tr>
<tr>
<td>Acitretin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Count</td>
<td>249</td>
<td>54</td>
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Disease-based registry (PSOLAR) reported that the most common types of serious infections were pneumonia and cellulitis. [9] Likewise, in the present study, the most common infections were respiratory tract infections followed by skin infections and UTIs.

In terms of the psoriasis subtypes, 50% of inverse, 42.5% of pustular, 24% of erythrodermic, and 15.3% of plaque-type psoriasis had a history of infection. In the present study, the chance of infection in patients with pustular psoriasis was 3.8 times higher than with other types; however, because of the low frequency of inverse psoriasis, the high frequency of infections in this group cannot be inferred.

Patients with psoriasis may be more susceptible to infections due to both the disease per se and the immunosuppressive medications. Previous studies have shown conflicting results about the correlation between different treatments and the risk of infection. The essential difference between the biologic and conventional treatments, using combination therapies, could be considered possible reasons for this discrepancy.

In our study, cyclosporine was significantly associated with FUO, although the overall risk of infection was not higher in contrast to Sejio et al., who reported a higher risk of overall and serious infections. [10] Likewise, prednisolone was associated with 2.93 times more frequent infections. Furthermore, we did not find any relationship between acitretin and infections, while Seijo et al. reported a lower risk of infection with acitretin. [10] These controversial results could be due to the predominant use of acitretin as a combination therapy with other drugs in the present study. Another controversial finding of our study was the lower risk of infection among patients treated with methotrexate, which is not in concordance with its immunosuppressive nature.

These controversies also exist in the prevalence of infections in psoriasis patients using biologic drugs. Hsu et al. stated that biologic treatments might increase the risk of

<p>| Table 4. The relationship between treatments and the most prevalent infection types. |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Methotrexate</th>
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<th>Cyclosporine</th>
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<td>OR</td>
<td>P-value</td>
<td>OR</td>
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<td>0.172</td>
<td>0.497</td>
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<td>0.032*</td>
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<td>common cold</td>
<td>0.755</td>
<td>1.37</td>
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<td>0.088</td>
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<td>0.703</td>
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</table>

*Negative correlation

Discussion

In the present study, we found that 21.5% of hospitalized psoriasis patients had at least one episode of infection; a total of 25 types were recorded in 111 patients. Men outnumbered women in this study, which may reflect more severe disease needing hospitalization in men. However, psoriatic women were more prone to infections.

In our study, the most common types of infection were pharyngitis (n=29), cellulitis (n=22), oral candidiasis (n=19), UTI (n=17), common cold (n=11), FUO (n=8) and pneumonia (n=7).

There was a significant correlation between age and oral candidiasis, UTI, and HSV. Previous studies have shown a higher prevalence of oral and cutaneous candida colonization and infection in psoriasis. [4, 5] Similarly, in the present study, oral candidiasis was the third most common infection, especially seen in the elderly; this may be partly attributed to dentures. Meanwhile, the older age of prevalence of UTI could be due to more common genitourinary problems in the elderly and lack of personal hygiene in this group.

We did not have precise details regarding the reason for the patients’ hospitalization, although it was primarily due to the psoriasis flare-up and not the infections per se. The most serious infections that led to hospitalization in this study were probably cellulitis followed by UTI.

In a Prospective Cohort Study from the British Association of Dermatologists Biologic and Immunomodulators Register, the most common types of infection in psoriatic patients were lower respiratory tract infections, followed by skin and soft tissue infections, and urinary tract infections. [6] While in a cohort study in the United Kingdom, upper and lower respiratory tract infections were the most prevalent. [7] In addition, a population-based cohort in the Netherlands showed that respiratory tract, abdominal, and skin infections occurred most frequently in patients with psoriasis. [8] Another study in a multicenter, longitudinal, disease-based registry (PSOLAR) reported that the most common types of serious infections were pneumonia and cellulitis. [9] Likewise, in the present study, the most common infections were respiratory tract infections followed by skin infections and UTIs.

In terms of the psoriasis subtypes, 50% of inverse, 42.5% of pustular, 24% of erythrodermic, and 15.3% of plaque-type psoriasis had a history of infection. In the present study, the chance of infection in patients with pustular psoriasis was 3.8 times higher than with other types; however, because of the low frequency of inverse psoriasis, the high frequency of infections in this group cannot be inferred.

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These controversies also exist in the prevalence of infections in psoriasis patients using biologic drugs. Hsu et al. stated that biologic treatments might increase the risk of
infection by controlling the inflammatory process and decreasing the disease severity or increasing this risk by suppressing the immune system. [11] In the present study, patients being treated with TNF-α inhibitors did not have any increase in infection risk, and even a lower risk of cellulitis was detected among patients using infliximab. Carneiro et al. [12] and Wakkee et al. [8] did not report any increase in infection risk in patients using biologic treatments compared with conventional drugs. Likewise, according to the Yiu et al. [13] and Garcia-Doval [14] studies, no increased risk of serious infections was found in patients on anti-TNF treatments. On the other hand, Yiu et al. have shown that infliximab was associated with a two-fold increased risk of serious infections compared with non-biologic treatments and a 3-fold increased risk compared with methotrexate. [15] Additionally, in a cohort study, Kalb et al. showed that serious infections were more likely to occur with adalimumab and infliximab than with non-biologic and non-methotrexate treatments. [9] Likewise, in three other studies, the authors found a higher risk of infection in biologic treatment compared with conventional treatments.

In recent studies, Systemic-immune inflammation index (SII) (neutrophil X platelet/lymphocyte) as a new complete blood cell index has been used in the prediction of disease progression and was associated with psoriasis activation and severity. Significantly higher SII values were present in higher PASI scores and indicated increased inflammatory response and poor prognosis. SII can also be an additional indicator of disease activation in autoimmune diseases such as Behçet’s disease. [16, 17]

Limitation
This retrospective survey was restricted solely to inpatient psoriatic cases admitted in the dermatology ward of a skin referral hospital. Therefore, information about patients treated in outpatient clinics and those hospitalized in general hospitals was unavailable. This study was conducted before the COVID-19 outbreak; therefore, it lacks data regarding the relationship between the risk of COVID-19 infection and the variables mentioned above.

Conclusion
Overall, 21.5% of psoriasis patients in the present study had at least one episode of infection. We observed an increased risk of infection in patients receiving prednisolone, while there was no increase in infection risk in patients treated with biologic drugs and even a relatively reduced risk in MTX-treated patients.

References


Evaluation of the Effect of Platelet-Rich Fibrin Matrix in the Correction of Periorbital Wrinkles: An Experimental Clinical Trial

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2 Shiraz Paramedical School, Shiraz University of Medical Sciences, Shiraz, Iran
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Key words: platelet-rich fibrin matrix, skin, cosmetics


Accepted: August 23, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

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ABSTRACT

Introduction: Skin rejuvenation techniques have gained substantial popularity due to increased life expectancy over recent years. Platelet-rich fibrin matrix (PRFM) is the new generation of platelet aggregate products that have surfaced in recent years to treat skin aging.

Objectives: We intend to use PRF to correct periorbital wrinkles in 15 volunteers and evaluate its effectiveness in this study.

Methods: To evaluate the efficacy of PRFM intervention, eight men and women over the age of thirty entered our study. Blood samples were taken and were immediately centrifuged at 700rpm for 5 minutes. PRFM was extracted from the plasma and injected at the sub-dermis site in periorbital areas. The initial severity of periorbital wrinkles was determined by Visioface 1000D, and obtained data were delivered to the statistical unit for statistical analysis. Scoring and evaluation were based on tissue volume and depth and were measured before and twelve weeks after injection. Adverse effects were also taken into consideration.

Results: The results demonstrated noticeable improvement in deep, fine, and small wrinkles, periocular hyperpigmentation, and overall skin freshness of the injection site. The subjects had swelling in the injection site for up to one day after the injection, which resolved without complications.

Conclusions: PRFM was observed to have potential in skin rejuvenation, demonstrating promising outcomes in terms of safety and long-term effects in improving skin condition.
Introduction

Throughout the years, concerns regarding skin aging have increased substantially, even affecting the young generations due to increased life expectancy [1]. The dermis, the inner layer of skin, which mainly consists of collagen and elastin, has the role of forming skin structure. The aging process destructs the elasticity of these fibers and reduces the production of hyaluronic acid; thus, skin aging results from a lack of elasticity, collagen bundle fragility, and fragmentation [2, 3]. Alongside intrinsic factors, environmental factors such as chemical exposure, ultraviolet radiation, smoking, and psychological changes also play a noticeable part in the aging process [3, 4]. Some studies have discussed the possible role of reactive oxygen species (ROS) in leading the skin aging process; however, despite the endeavors to discover the underlying mechanism, its pathogenesis is yet to be fully comprehended [5].

Skin aging is categorized into two subgroups, which are intrinsic and extrinsic aging. Intrinsic aging progresses with age and can be described by epidermal thinning and fine wrinkles. However, deep wrinkles, hyperpigmentation, and skin laxity can be observed in extrinsic skin aging, which is greatly impacted by chronic sun exposure. All in all, skin wrinkles are the hallmark of skin aging [4, 6].

In recent years, many exogenous filler materials have been put to the test in the hope of improving skin wrinkles by volume augmentation. The mainstay of filler disadvantages is its absorbable nature, which reduces its effect over time. Among these methods, platelet-rich plasma (PRP) injection has recently attracted significant attention. PRP consists of concentrated platelet and growth factors obtained via venous blood centrifuge [7]. Platelet-rich fibrin matrix (PRFM) is the new PRP generation that is richer in growth factor concentration, enabling it to have a significantly better outcome in stimulating angiogenesis, tissue regeneration, and wound healing. Moreover, PRFM induces mesenchymal stem cell (MSC) migration to the site of injection, which bears imperative regenerative function [2].

Currently, various exogenous fillers are utilized globally, including in Iran. High cost, owing to the exogenous nature of the filler and transient side effects such as edema, erythema, encapsulation, granuloma formation, and even chronic or delayed infection, minimizes its popularity [8]. Conclusively, PRF as a natural autologous filler has the potential to be a safe candidate with long-lasting effects.

Objectives

Several studies have concluded that PRF is an effective route in reducing skin wrinkles with minimal side effects. Its side effects are mainly limited to transient erythema at the injection site [9]. This study intends to use PRF to correct periorbital wrinkles in 15 volunteers and evaluate its effectiveness.

Methods

Study Design and Participants

In this prospective clinical trial, sixteen adult women and men over the 30-year-old with facial wrinkles who volunteered to participate were included in the study. Participants were excluded in cases younger than 30 years old, significant past medical history, such as connective tissue disorder, myocardial infarction, hypertension, pregnancy, and use of immunomodulatory or anticoagulation (e.g., Aspirin, Warfarin) medication. The purpose of the study and all side effects of the intervention were clearly explained to all participants. They were assured their information would remain confidential, and they were permitted to withdraw from the study if they requested. Subsequently, written informed consent was obtained from all patients. The sample size was estimated based on a study by Sclafani et al [10], based on the mean wrinkles assessment score before and after the intervention, taking into account the first type error of 5%, 80% power, and an effect size of 0.8, calculating to a total of 15 participants.

Intervention

For intervention, after evaluating the patient’s medication and drug history, the total depth of wrinkles before injection was measured with the Visophysics device. Decosept and a tourniquet were applied, and a 15cc blood sample was taken with a syringe at a 15-degree angle from the brachial vein, transferred to three 5cc tubes, and immediately centrifuged at 700 rpm for 5 minutes. Then, using a canola, except for 1 cm above the tubes, the rest of the plasma, which had a gel-like consistency, was transferred to a 5-cc sterile syringe. After this, PRF was transferred to 1 cc syringes by sterile connection. Simultaneously with the beginning of the blood collection process, local anesthesia (Xyla P Cream, Tehran Chemie) was used at the injection site. The duration of local anesthesia was at least 30 to 50 minutes, based on the patients’ anesthesia capacity. After sterilizing the injection site with betadine, a 3cc PRF solution was injected into the wrinkles around the eyes with a canula number 27 on both sides. The injection was performed at the sub-dermis site and in one session. The patients were advised to visit our clinic in case of delayed alleviation of swelling or adverse effects, such as infection. Also, since the effectiveness of PRF was to be evaluated in our study, the use of creams or other products was not recommended. Participants were also informed that they could also be present at work on the same day of the procedure without any problems.
Outcome Assessment
The initial severity of periorbital wrinkles was determined by Visioface 1000D (CK electronic, manufactured in Germany), and obtained data were delivered to the statistical unit for statistical analysis. Scoring and evaluation were based on tissue volume and depth and were measured before and twelve weeks after injection. Patients were also advised to visit in case of developing any complications.

Data Analysis
Data were entered into SPSS version 21 and subsequently analyzed. An independent sample t-test was used to evaluate the difference in tissue volume among the groups. A P-value of less than 0.05 was considered statistically significant.

Ethical Considerations
The study was approved by the Research Ethics Committee of the Shiraz University of Medical Sciences and was conducted in compliance with the relevant guidelines and regulations and the Declaration of Helsinki. Written informed consent was obtained from the patients in our study. The purpose of this research was completely explained to the patients, and they were assured that their information would be kept confidential by the researcher. The present study was approved by the Medical Ethics Committee of the academy (Ethical Code: IR.SUMS.MED.REC.1400.480) and registered in the clinical trials database (Code: IRCT20220218054054N1).

Results
Sixteen patients, consisting of eight males and eight females, were included in our study. Each participant was evaluated based on changes in the left and right side periorbital wrinkles after PRF injection. The subjects had swelling in the injection site for up to one day after the injection, which resolved without complications. We measured tissue depth with a Visophysis device before and twelve weeks after injection. During this period, none of the people had any complications and all were completely satisfied. The tissue volume score of the participants included in our study is demonstrated in Figure 1. Also, Figure 2 demonstrates the cosmetic appearance of the results of our study.

There was no significant difference among the male and female groups regarding tissue volume before injection at both sides. (P=0.964 and 0.240 for right and left, respectively). Furthermore, As demonstrated in table 1, the tissue volume size on both sides significantly decreased, both in males and females, after PRF injection (Table 1). However, there was no significant difference among males and females regarding tissue volume after injection (P=0.784 and 0.427, for right and left, respectively) or amount of tissue volume change (P=0.828 and 0.0339, for right and left, respectively)

It should be noted that following PRF injection, in addition to improving deep wrinkles, noticeable improvement was observed in fine and small wrinkles, periocular hyperpigmentation, and overall skin freshness of the injection site. All subjective reports among our participants reported satisfaction and were eager to repeat and recommend this procedure.

Discussion
In recent years, platelet concentrates injection has gained global popularity, which, combined with the increased demand for skin rejuvenation techniques, calls for further clinical assessment of the safety and function of these products. PRF is the new evolutionary face of platelet-rich aggregates [11]. This study puts the effect of PRF under conduction and observed significant improvement in periorbital skin rejuvenation accompanied by significant patient satisfaction.

![Figure 1. Changes in tissue volume before and after platelet-rich Fibrin injection among females (patients 1 to 8) and males (patients 9 to 16).](image-url)
device. The results revealed significant improvement in deep wrinkles in all candidates. Furthermore, noticeable improvements were also noted in fine and small periorbital wrinkles. This result is also in line with previous studies on the benefits of PRF [11].

Along with the diminishing wrinkles, improvement in skin hyperpigmentation and overall freshness were also of significance. Maisel-Campbell et al. conducted a systematic review of the benefits of PRP injection and observed significant improvement in skin texture through different studies [14]. A Chinese study conducted on the effect of PRP injection also concluded that skin quality was significantly enhanced in participants with a substantial decline in wrinkles, pores, and texture. Furthermore, PRP treatment was detected to inhibit UV-B-induced tyrosinase and metalloproteinase-1 (MMP-1) upregulation, which along with tropoelastin and fibrillin induction, results in photoaging enhancement [15].

The benefits of platelet aggregate products take root from not only its high concentration of growth factors, but also its gelatin constituents. The gelatin part has the potential to bring elasticity and a good support system for wrinkles, cavities, and skin relaxation [16]. In addition, these platelet aggregate products contain cell adhesion proteins PRF, the second generation of platelet concentrates, is superior to PRP in numerous aspects. First of all, PRF preparation consists of only one centrifugation step, making it simpler than PRP preparation [12]. As a result of declined centrifuge speed, PRF has been observed to contain higher volumes of growth factors, leukocytes, fibrin, and platelets than PRP, resulting in a more boosted growth factor-mediated functional aftermath [11]. Secondly, PRF is completely autologous and does not contain any exogenous additives, which supports the natural physiologic polymerization of fibrin. Growth factor binding and platelet capture are facilitated via the three-dimensional fibrin structure of PRF that results in the enhancement of the gradual and long-term release of cytokines and growth factors. Moreover, this fibrin mesh is also responsible for cell proliferation and differentiation and the formation of new blood vessels [11, 12]. Finally, PRF prompts cell proliferation, migration, differentiation, and adhesion accompanied by anti-inflammatory properties that further support its therapeutic aptitude in bone regeneration, wound healing, improving scar appearance, and stimulating hair growth [2, 13].

This study utilized a PRF solution for periorbital wrinkles, and the depth of the wrinkles was assessed via a Visophysis device. The results revealed significant improvement in deep wrinkles in all candidates. Furthermore, noticeable improvements were also noted in fine and small periorbital wrinkles. This result is also in line with previous studies on the benefits of PRF [11].

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**Table 1. Tissue volume score and changes based on gender and laterality.**

<table>
<thead>
<tr>
<th>Gender</th>
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<td>After</td>
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<td>11.00 ± 3.59</td>
<td>3.88 ± 3.94</td>
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<td>13.13 ± 3.23</td>
<td>10.50 ± 2.88</td>
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<tr>
<td>Male; n=15</td>
<td>15.00 ± 4.75</td>
<td>11.50 ± 3.59</td>
<td>3.50 ± 2.73</td>
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<td>15.75 ± 5.12</td>
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<td>P-value*</td>
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<td>0.784</td>
<td>0.828</td>
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<td>0.240</td>
<td>0.427</td>
</tr>
</tbody>
</table>

* Independent sample t-test

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![Figure 2. Results of platelet-rich fibrin matrix in the correction of periorbital wrinkles.](image)
which could help keep the skin tight and smooth [15]. The decline in hyperpigmentation that was observed in our study is consistent with previous studies and is due to the fact that platelet aggregate products increase skin thickness and ameliorate collagen content which results in reduced pigmentation [11, 14, 15].

The patients in the present study had a 12-week follow-up session to evaluate their skin quality post-PRF injection. The periorbital wrinkles, skin hyperpigmentation, and overall freshness were held down, therefore, adding support to the long-term effect of the PRF procedure. Liang et al. did a 6, 12, 24-month follow-up after nano fat-PRF injection and observed that patient satisfaction was of significant worth even after the 12-month mark [4]. All in all, these findings shed light on the PRF’s potential as a long-term and safe skin rejuvenating technique.

Skin aging can substantially impact each individual’s quality of life. Youth, health, and activity are three major ideals that are starting to grow in the community’s lives. Therefore, skin wrinkles can have psychosocial outcomes in people’s lives. A study conducted in Germany concluded that those who underwent cosmetic procedures had higher quality of life [17]. Conclusively, PRF as a potent procedure for skin rejuvenation may, in turn, advance the quality of life in the population.

Throughout our study, adverse effects of PRF were taken into consideration, and the reports were promising as no adverse effects were seen other than the first-day injection site edema. This finding was in line with previous studies [11]. Over the literature, no major adverse reactions were reported, and the side effects are observed to be only limited to slight bruising in the injection site [4, 11, 18].

Some limitations should be addressed. Due to the Covid-19 pandemic, patients were only evaluated after 12 weeks, and frequent visits were not applied, limiting our statistical power for the clinical outcomes assessment, while no objective documentation of their satisfaction was carried out. However, all patients reported satisfaction and were eager to repeat and recommend this procedure. Additional limitations include the relatively limited number of participants and the treated areas.

Conclusion

In summary, this study demonstrated that intradermal PRF injection could be considered as a safe, long-term technique accompanied by favorable objective facial skin rejuvenation and improving patient satisfaction. Along with diminishing wrinkles, improvements in skin hyperpigmentation and overall freshness were also of significance. However, further longitudinal studies need to be carried out to assess the long-term outcomes of PRF injection. Also, studies with higher sample sizes are warranted to understand the extent of improvement and also possible side effects.

References


Limited Access to Dermatology Specialty Care: Barriers and Teledermatology

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Key words: barriers, teledermatology, melanoma, non-melanoma, skin cancer

Citation: Duniphin DD. Limited Access to Dermatology Specialty Care: Barriers and Teledermatology. Dermatol Pract Concept. 2023;13(1):e2023031. DOI: https://doi.org/10.5826/dpc.1301a31

Accepted: April 17, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

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ABSTRACT

Introduction: Access to dermatology specialty care is limited in the underserved population. Barrier identification and exploring the potential role of teledermatology are the first steps to address this problem.

Objectives: Identify the barriers to dermatologist care for the diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population. Additionally explored was the potential role of teledermatology to provide dermatology care access in the underserved population.

Methods: A quantitative descriptive study was conducted via an online survey instrument. The survey’s barriers portion was adapted from the 1998 Ohio Family Health Survey (OFHS). The survey’s teledermatology portion was adapted from the McFarland Teledermatology Provider and Imaging Technician Satisfaction Survey. The participants were practicing dermatologists and members of Georgia, Missouri, Oklahoma, and Wisconsin dermatology associations. Thirty-eight responded to demographic questions, of which twenty-two responded to the survey items.

Results: The top three barriers ranked as the most concerning were “continually uninsured” (n = 8; 36.40%), “resides in a medically underserved county” (n = 5; 22.70%), and “family under federal poverty level” (n = 7; 33.30%). Teledermatology as a potential role for access to care was supported by convenient delivery of healthcare (n = 6; 72.70%), an addition to regular patient care (n = 20; 90.90%), and increase to patient care access (n = 18; 81.80%).

Conclusion: Barrier identification and teledermatology access to provide care to the underserved population is supported. Further teledermatology research is necessary to address the logistics regarding how to initiate and deliver teledermatology to the underserved.
Introduction

Access to dermatology specialty care is limited in the underserved population and is related to patient socioeconomic status, rural residence status, and provider location distribution [1]. Melanoma and non-melanoma skin cancer in the underserved population have public health repercussions that include poor patient outcomes directly associated with late-stage diagnoses [2]. Barrier identification and dermatology access are the first steps to address the dermatological needs of the underserved population. It is estimated that a 16% increase will occur between 2013 and 2025 for dermatology visits [3]. There are approximately 3.4 dermatologists per 100,000 population, which is lower than what is needed to provide adequate dermatology care in communities [4]. This overall dermatology access shortage includes 67.10% in dedicated medical dermatology patient care time [5]. The combination of the rise in skin cancer rates, extended wait times, increased need for dermatology visits, and the shortage of practicing dermatologists prompts a valid public health concern. This concern is exacerbated by barriers to care for the underserved. Innovative methods are necessary for patients to have sufficient access to dermatologist care [5].

Teledermatology allows providers to diagnose and recommend treatment and address the limited dermatology specialty care access in the underserved population. One of the main telemedicine applications is to triage dermatology patients with higher morbidity and mortality risks to facilitate earlier in-person visits [6]. This access accommodates early detection of potentially lethal dermatological diseases such as melanoma and non-melanoma skin cancers. The barrier-focused framework included patient income, lack of insurance, and where the underserved population seeks health care. The poor, those who live in rural areas, and high minority locations lack access to dermatologists [1]. There is a need for additional research-tested programs for dermatologic treatment for underserved communities [2]. To address and explore potential treatment intervention programs, barrier identification for dermatologist care of skin cancers in the underserved population is necessary in closing the gap of dermatologic specialty care of melanoma and non-melanoma skin cancers to the underserved population. Current research also includes the use of teledermatology for general dermatology care; however, there is a scarcity of teledermatology to provide access for diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population.

Early detection that leads to earlier diagnosis and treatment of melanoma and non-melanoma skin cancers improves patient care outcomes and reduces morbidity and mortality [7]. Barrier identification is the first step to find and improve interventions to address and resolve these obstacles.

Objectives

The purpose of this quantitative descriptive study was to identify the barriers to dermatologist care for diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population. Additionally explored was the potential role of teledermatology to provide access to this care in this population.

Methods

The research design was a quantitative descriptive study via a survey instrument. The study participants were practicing dermatologists who were members of either Georgia, Missouri, Oklahoma, or Wisconsin dermatology associations. The respective state dermatology associations sent the surveys to the memberships. The accessible population included 700 dermatologists. The estimate of this population size with a confidence level of 95%, a margin of error at 5%, and the estimated 10% response rate indicates 248 participant responses was the optimal sample size [8]. A total of 38 responded to demographic questions, of which 22 responded to the survey items. The cover letter served as the survey participation invitation with the inserted SurveyMonkey link. Survey responses were anonymous with computer password protection. The survey data collection range was February 2019 – April 2019. The inclusion criteria were (a) a practicing dermatologist who is a member of his or her respective state dermatology association in the states of Georgia, Missouri, Oklahoma or Wisconsin; and (b) between the ages of 25 through 64. The exclusion criteria were (a) a non-practicing dermatologist in any state and (b) below the age of 25 or above the age of 64. The sampling methodology was quantitative. The sampling methodology was non-probability consecutive sampling.

The barriers portion of the survey was adapted from the 1998 Ohio Family Health Survey (OFFS), which was developed through the Ohio Department of Health [9]. Ten rank-order barriers were adapted regarding access to dermatological specialty care. Permission to use and adapt the data collection tool, “McFarland Teledermatology Provider and Imaging Technician Satisfaction Survey” was requested, approved, and received by the author Dr. Lynne McFarland. Nineteen items on a 5-point Likert scale were adapted for the teledermatology items. The demographic portion of the survey included dichotomous, classificatory, and rank-order responses. The demographics included age, sex, degrees, income, and race. Also included in the demographics were practice setting, practice-setting location, and if the participant had received training in teledermatology.

The validity and reliability of the “McFarland Teledermatology Provider and Imaging Technician Satisfaction Survey” was requested, approved, and received by the author Dr. Lynne McFarland. Nineteen items on a 5-point Likert scale were adapted for the teledermatology items. The demographic portion of the survey included dichotomous, classificatory, and rank-order responses. The demographics included age, sex, degrees, income, and race. Also included in the demographics were practice setting, practice-setting location, and if the participant had received training in teledermatology.
Survey” was based on the validated PSQ originally developed by Ware et al. that classifies similar items [10]. The questions were from a standardized, validated, and reliable instrument (Cronbach’s alpha = 0.72-0.92 over the domains for internal consistency) and construct validity regarding multiple patient settings. According to McFarland, this instrument was for telemedicine in general, but not specifically teledermatology. McFarland’s questions were dermatologist and medical provider vetted for concerns and satisfaction areas [10]. The satisfaction domains were recommended by a review of Kraai et al. telemedicine satisfaction surveys [10]. Two dermatologist subject-matter experts were enlisted to establish face and content validity for this study’s survey. The feedback included the addition of the practice setting to specify academic, private, or hospital, and the practice setting location to specify urban, rural, or suburban. Feedback also included if the participant had teledermatology training.

Descriptive statistical analysis was conducted using IBM SPSS Statistics Version 25. Frequencies and percentages were reported for nominal demographic variables. Frequencies, percentages, median, and IQR were reported for ordinal demographic variables. Ratio level data were tested for normality using the Shapiro-Wilk test (p < .05) and the median and IQR were reported. The barriers were rank-ordered with frequencies and percentages noted. A 5-point Likert scale was used to rate the responses of the teledermatology items. Because the statements were adapted from a standardized data collection instrument and not all of the original questions were included, an item-by-item analysis was conducted. Frequencies and percentages were reported for the teledermatology items as well. Findings for rank-ordered barriers and teledermatology items were included both in text and in a tabular format.

Results

An estimated 700 potential participants received the survey via the four dermatologist societies. Thirty-eight participants responded to demographic questions. Of the 38 respondents, 22 responded to the survey items. The remaining 16 surveys were excluded due to not meeting inclusion criteria or not answering the barrier or teledermatology item sets. The approximate number of participants that received surveys was 700, which represents a 5.43% overall response rate. The complete survey response rate was 3.14%. Testing for normality for the age demographic was completed by using the Shapiro-Wilk test (p = .005). The median age was 54 (IQR = 17) years (see Table S1). The majority of the respondents were male (n = 13; 54.20%), and most held MD degrees (n = 25; 65.80%). Annual income was tested for normality using the Shapiro-Wilk test. The median income was $200,000 or more (IQR = 0). Most practice settings were private (n = 24; 96.00%), and the location setting majority was suburban practice (n = 15; 60.00%). Most dermatologists did not have teledermatology training (n = 14; 56.00%) (see Table S1).

Research question 1. The first research question addressed the rank-ordering of the barriers to dermatologist care for the diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population. Ten barriers were rank-ordered by the respondents in order of greatest to least concerning barrier (see Table S2). The top three barriers ranked as the most concerning were “continually uninsured” (n = 8; 36.40%), “resides in a medically underserved county” (n = 5; 22.70%), and “family under federal poverty level” (n = 7; 33.30%), respectively (see Table S3).

Research question 2. The second research question addressed the potential role of teledermatology in providing access to dermatologist care for the diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population. The respondents rated each statement on a 5-point Likert scale ranging from strongly disagree = 1 to strongly agree = 5. The scale ratings were collapsed to produce a dichotomous response for each statement item. Strongly disagree and disagree were combined as well as strongly agree and agree were combined. No opinion was removed from the analysis results to maintain dichotomous results (see Table S4).

This study found that the major barriers to the diagnosis and treatment of melanoma and non-melanoma in the underserved population were related to insurance status, medically underserved county residence, and income level. The greatest barrier was “continually uninsured patients”, followed by “resides in a medically underserved county”, and “family under federal poverty level”. The results regarding the barriers of “resides in a medically underserved county”, and “family under federal poverty level” support the research by Vaidya that the poor access to dermatology specialty care in the underserved population is related to patient socioeconomic status, rural residence, and provider location distribution. Research results by Campagna et al. [11] additionally support that limited access to dermatology specialists is due to rural residence and socioeconomic barriers in the underserved population. The highest-ranked barrier of continually uninsured identified in this study supports the research of Nelson et al. [12] that uninsured, Medicaid, and rural patients have increased wait times for dermatology office visits. The appointment waiting time for this population to see a dermatologist delays diagnosis and subsequent treatment. This result is also supported by the research of Pasquali et al. [13] that a benefit of teledermatology provided dermatology specialty care access to patients in remote areas and patients on long waiting lists.
The conceptual barrier-focused framework included the lack of insurance, where the underserved population seeks healthcare access, and patient income, which was supported by this study’s findings. The status of the patients’ health, insurance, and income was among barriers associated with the lack of a regular healthcare source [9]. Barrier identification is the first step to resolve access and care. Innovative methods are necessary for patients to have sufficient access to dermatologist care [5].

This study also found that the role of teledermatology in providing access to dermatological specialty care for diagnosis and treatment of melanoma and non-melanoma is a viable option in the underserved population. This finding supports Levitt et al. [6] that using teledermatology in the underserved population increases access to care for this population. The results of this study found that dermatologists agreed regarding the ability to describe and assess dermatology diagnoses and treatment needed as well as monitor the patients’ conditions via teledermatology. These findings agree with Leavitt et al. [6] that teledermatology contributes to accurate diagnoses with consistency. Teledermatology could increase access to dermatology care, which would ease the ability for patients to contact a dermatologist. The increase in access is supportive of earlier patient care, which could benefit earlier skin cancer detection. These results also support the premise of Apalla et al. [7] that early detection leads to early diagnosis and treatment of melanoma and non-melanoma skin cancers and improves patient care outcomes, reducing morbidity and mortality. Research by Fludiona et al. [14] provides additional support regarding early detection, reporting that suspicious neoplasms were the top diagnosis that recommended accelerated face-to-face consultation for teledermatology patients. Teledermatology is the clinical diagnostic technology of choice for patients who have concerning lesions with access barriers to care per Skudalski et al. [15].

Teledermatology was found to be a convenient form of healthcare delivery and a standard form of healthcare delivery for the future. These results support Nelson et al. [12] that teledermatology complements outpatient dermatology healthcare delivery. This study found that dermatologists were willing to add teledermatology to the regular patient care received and agreed there was no threat to patient confidentiality and privacy. These results support McFarland et al. [10] also showing majority agreement in the same areas. The results of this study indicated that the logistics of using the camera and computer in teledermatology were not difficult; however, trusting the equipment to work was a concern. These results were in agreement with McFarland regarding whether the equipment was easy to use; however, it was in opposition regarding whether the equipment was trusted to work. The findings in this study showed that the preference was face-to-face patient visits over teledermatology, and the lack of physical contact for the physical exam was a concern. These results did not support McFarland, which reports a slight preference for teledermatology over face-to-face visits, as well as the lack of physical contact, which was sufficient. The results of this study included the recognition of the need for access and care for the underserved population, which supported Jacobsen et al. [2] showing there is a need for additional research-tested programs for the treatment of the underserved population.

The sample size of this study was relatively small compared to the number of U.S. dermatologists. The small sample size limits the generalizability of this study, and the results are suggestive to the population.

The findings of this study identified and rank-ordered the barriers to the diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population. These identified findings can be addressed by healthcare providers and administrators to begin to overcome these barriers for patients. The results also indicate that there is a potential role for teledermatology to provide access to dermatology specialty care. These findings can also be used by healthcare providers and administrators to not only address the barriers but to begin the logistical and financial process to provide teledermatology services. By opening the dialogue of barrier identification and teledermatology potential, dermatology diagnosis and treatment of melanoma and non-melanoma skin cancers can result in better patient care and outcome.

A limitation of this study was the small sample size, which reduced the generalizability of the study results. The sampling method was also a limitation, as it did not reach a large enough number of practicing dermatologists. Due to the time allotted for this study, a limitation was also addressing two different research questions as opposed to one. Even though they are related to each other, separate studies would allow greater focus and more in-depth research for each question.

Recommendations for future research include attempting to resolve the limitations discussed for this study, such as obtaining a larger sample size by additional participant requests and devoting more research time. A recommendation for research includes exploring the logistics and costs associated with providing teledermatology to the underserved as well as patient transportation for follow up face-to-face visits. The cost and payment of treatment, how to initially launch teledermatology, and operational requirements also need to be researched to address the need for care of the underserved. This research process has shown that each item identified opens up new avenues to be explored and studied.
Conclusion

The purpose of this study was to identify the barriers to the diagnosis and treatment of melanoma and non-melanoma skin cancers in the underserved population, as well as the potential role of teledermatology to provide access to dermatologist care. The most concerning barriers, namely “continually uninsured”, “resides in a medically underserved county”, and “family under federal poverty level”, prompt the need for additional research to address and overcome these barriers. These barriers raise public issues of affordable health care, healthcare provider incentive to practice in underserved locations, and the effect of poverty regarding healthcare. There is support for the potential role of teledermatology to provide dermatology care for the underserved. Even though dermatologists did prefer face-to-face visits over teledermatology as well as a concern for lack of physical contact, the remaining results support teledermatology use. Access barriers are also concerning in other countries including India, Madagascar, and Senegal due to a low dermatologist-to-population ratio. [13]. In addition to identifying barriers to specialty dermatology access for the underserved population, teledermatology includes training to cover basic dermatological conditions on a global scale [13]. Within the scope of this study, the access-to-care barriers regarding general skin care versus specialty dermatological care are the same, as the focus is in regards to the underserved population. Further research is needed to address the logistics to initiate and deliver teledermatology to the underserved, as well as the costs to provide access, treatment cost, and patient transportation. In summary, identifying the barriers as the first step to providing dermatology care for the underserved raises the need for more research to address and find resolutions. The role of teledermatology to provide access is supported, but there is also a need for further research to explore the logistics and costs to provide this service to the underserved.

Acknowledgment: Helen Salisbury, PhD, A.T. Still University, Mesa, Arizona, United States

References

Clinical and Histopathological Evaluation of Forty-one Cases of Pediatric Granuloma Annulare

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Key words: Granuloma annulare, asthma, histopathology, interstitial type, palisadic type

Citation: Koku Aksu AE, İlhan Erdil D, Manav Baş V, Büşra Türk C, Leblebici C, Tellal ES. Clinical and Histopathological Evaluation of Forty-one Cases of Pediatric Granuloma Annulare. Dermatol Pract Concept. 2023;13(1):e2023113. DOI: https://doi.org/10.5826/dpc.1301a113

Accepted: January 4, 2023; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Granuloma annulare (GA) is a non-infectious granulomatous disease that can affect children and adults. Although many studies have been conducted in adult GA patients, the literature on pediatric GA cases is limited.

Objectives: Therefore, this study aimed to examine the demographic, clinical, and pathological features of pediatric GA cases.

Methods: This study was performed retrospectively in a single-center tertiary dermatology hospital. Demographic characteristics and clinical and histopathological features were recorded.

Results: Forty-one participants were included in this study, of which 66% were females. The mean age was 3.8 ± 2.6 years, and the mean lesion duration was 7.5 ± 10.3 months. The involvement of 78% of the patients was localized, and the remaining 22% was generalized. Asthma (30%) was the most common comorbid disease. Histopathological examination was performed on 21 patients, and the infiltrate pattern was interstitial in 71% of the cases and palisadic in 29%. Generalized distribution, trunk involvement, and concomitant disease tended to be higher in patients with an interstitial pattern than in those with a palisadic pattern.

Conclusions: Atopy and asthma should be questioned in pediatric GA cases. There are differences between involvement, distribution, concomitant disease, and histopathological patterns, which may indicate differences in pathogenesis.
Introduction

Granuloma annulare (GA) is a non-infectious granulomatous skin reaction with potential triggers that can affect adult and pediatric populations. The etiology of GA is unknown, but medication, infection, trauma, insect bites, and vaccination have been reported as triggering factors [1–3]. Solitary, erythematous, annular papules, and plaques are found predominantly in the acral regions. Histopathologically, collagen degeneration, mucin deposition, and lymphohistiocytic infiltrate are typically observed [4]. Diabetes mellitus, hyperlipidemia, and malignancy have been associated with adult GA [5–6].

Objectives

While there are many studies on clinical and pathological features and associated diseases in patients with adult GA, few studies have examined pediatric GA patients. Therefore, clinical and histopathological evaluations of pediatric GA cases were planned for our study.

Methods

This study was performed retrospectively in a single-center tertiary dermatology hospital in Istanbul. Ethical approval was obtained from the Clinical Research Ethics Committee of the Istanbul Training and Research Hospital on 11/03/2022 (2011-KAEK-50). Patients under the age of 18 years who were admitted to the dermatology outpatient clinic between 2008–2021 and diagnosed with GA were scanned from the hospital database and patient photograph archive. Cases with an uncertain diagnosis were excluded. Written informed consent was obtained from the parents of the patients participating in the study. Cases with dermatological findings recorded in detail and/or diagnosed histopathologically were included in the study. In total, 41 patients diagnosed with GA were included. Demographic features, lesion localization, lesion characteristics (size, elementary lesion, and color), involvement (localized/generalized), histopathological features, concomitant diseases, differential diagnoses in cases with histopathology, regression time, and recommended treatments were recorded. Missing data were questioned by calling the patients by phone. Age- and gender-matched patients of the pediatric outpatient clinic were included in the study as the control group to evaluate comorbidities.

Statistical analyses were performed using SPSS version 23.0. The conformity of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov–Smirnov/Shapiro–Wilk tests. The mean, standard deviation, median, minimum, and maximum values were used when presenting the descriptive analyses. The Mann–Whitney U test was used when evaluating normally distributed (parametric) and non-normally distributed (non-parametric) variables between the two groups. When presenting the categorical variables, the frequency and percentage values of the variables were used, and the analysis of the categorical variables was carried out using the chi-squared (exact) test. The Bonferroni multiple comparison test was used to investigate the reason for the significant differences between the groups. Cases with a P value below 0.05 were considered statistically significant.

Results

Forty-one participants were included in this study, 66% of which were females. Their mean age was 3.8 ± 2.6 years, and their mean lesion duration was 7.5 ± 10.3 months. Seventy-eight percent of the patients had localized GA (LGA), while the remaining 22% had generalized GA (GGA) (Figure 1). The lower extremities were the most commonly affected area, and the most common type of lesion was the plaque type (79%). The mean size of the lesions was 3.8 ± 1.9 cm (Table 1). There was no statistically significant difference between clinical criteria and gender (P > 0.05). However, upper extremity involvement was significantly more common in patients with GGA compared to those with LGA (P < 0.004). No significant differences were found between GGA and LGA in terms of other parameters.

Information on the concomitant diseases was evaluated in 30 of the 41 cases. The evaluation found the following: accompanying disease (30.0%, N = 9), asthma (10.0%, N = 3), and one case each of atopic dermatitis, autoimmunity (type 1 diabetes mellitus, Hashimoto thyroiditis), congenital heart disease, pustular psoriasis, and thalassemia. In addition, information on the concomitant disease was evaluated in 146 patients in the age- and gender-matched control group, which resulted in the following: asthma (3.4%, N = 5), hypothyroidism (1.4%, N = 2), atopic dermatitis (0.7%, N = 1), and plaque-type psoriasis (0.7%, N = 1).

The most common differential diagnoses in GA cases were sarcoidosis, tinea corporis, and erythema annulare centrifuge, respectively. Histopathological examination was performed on 21 patients (Table 2). The infiltrate pattern was interstitial in 71% of the cases and palisadic in 29% (Figures 2 and 3). Eosinophil infiltration was observed in 19% of the cases, and lymphohistiocytic infiltration was observed in 90%. Eosinophils were detected in the histopathological examinations of 4 patients, and in 2 of these cases the presence of concomitant asthma was also noted. Trunk involvement was detected in 5 (33%) out of 15 patients with an interstitial pattern, but it was not detected in any of the patients with the palisadic pattern. The difference was statistically significant (P = 0.01). All palisadic patterns (N = 6) were LGA, and 6 (40%) of those with interstitial patterns
showed GGA. However the difference was not statistically significant (P > 0.05). Concomitant disease was present in 5 (33%) out of 15 patients with the interstitial pattern, but it was not detected in any patients with the palisadic pattern.

All of the treated cases received a topical steroid, and the mean duration of the lesions after treatment was 6 ± 5.4 months. When 28 (68%) out of the 41 cases were reached by phone, complaints were still present in 14% (N = 4). The disease regressed in 86% of the cases within one year.

Conclusions

GA can be observed in pediatric and adult populations; however, there are limited data about demographic, clinical, and histopathological features and associated diseases in pediatric GA patients.

In this study, female predominance was evident (66%), similar to adult cases [7]. Notably, male predilection was apparent in two pediatric GA case series [8,9], and no gender difference was detected in another study [10]. Hyperlipidemia and diabetes have been found to be the most common comorbidities in adult GA [5,6]. In our study, unlike in adult GA case series, asthma was found to be the most common accompanying disease.

In our study, 10% of the patients with GA had asthma, a higher rate than the control group (3.4%). Additionally, 13% of the GA cases had atopy (atopic dermatitis and asthma). Previous research has reported even higher rates of atopy (up to 30%) in GA cases [9]. However, to the best of our knowledge, the relationship between pediatric GA and asthma has not been previously reported. The presence of asthma, which is a characteristic of atopic march, suggests that these patients should be evaluated for other atopic conditions such as atopic dermatitis, and allergic rhinitis.

The coexistence of GA and atopy may indicate a common pathogenesis. In recent years, it has been shown that in addition to T-helper 1 and T-helper 2 cell types, the Janus Kinase-Signal Transducer Transcription Activator (JAK-STAT)
histiocytes, while an interstitial pattern comprises histiocytes localized to the papillary or middle dermis distributed between collagen fibers and blood vessels [16]. There is a paucicellular appearance, with minimal mucin traces in the interstitial pattern [17].

In this study, histopathological examination of 21 patients was performed. The histopathological pattern was palisading in 6 patients, while the remaining (N = 15 patients) showed interstitial pattern. Trunk involvement was detected in 5 (33%) out of 15 patients with an interstitial pattern, but it was not detected in any patients with a palisadic pattern. Another striking finding was that all of the palisadic patterns were LGA, and 6 (40%) of those with an interstitial pattern showed GGA. The concomitant disease was present in 5 (33%) out of 15 patients with an interstitial pattern, whereas none of the patients with a palisadic pattern had concomitant disease. As a result, trunk involvement, GGA,

### Table 1. Descriptive statistics of demographic, clinical, and treatment features of pediatric granuloma annulare cases.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gender, N (%)</th>
<th>Age, years, mean ± SD /median (min–max)</th>
<th>Lesion duration, months, mean ± SD /median (min–max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girl</td>
<td>27 (66)</td>
<td>3.8 ± 2.6 (3.00 (1.0–12.0))</td>
<td></td>
</tr>
<tr>
<td>Boy</td>
<td>14 (34)</td>
<td>4.00 (1.0–54.0)</td>
<td></td>
</tr>
<tr>
<td>Localization, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity</td>
<td>14 (34.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremity</td>
<td>30 (75.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>7 (17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluteal</td>
<td>3 (7.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary lesion, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papule</td>
<td>5 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodule</td>
<td>1 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch</td>
<td>6 (17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque</td>
<td>27 (79.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light brown</td>
<td>1 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>9 (39.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purple</td>
<td>1 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pink</td>
<td>11 (47.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>1 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean size of the lesions (cm), ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involvement, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>32 (78.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>9 (21.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant disease, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>3 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
<td>1 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pustular psoriasis</td>
<td>1 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>1 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>1 (3.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; SD = standard deviation.

### Table 1. Descriptive statistics of demographic, clinical, and treatment features of pediatric granuloma annulare cases.

pathway is involved in the pathogenesis of GA [11]. Treatment with JAK-STAT inhibitors resulted in the downregulation of cytokine levels and clinical improvement in GA [12]. In addition, topical JAK-STAT pathway inhibitor administration is clinically effective in the treatment of GA [13]. The pathway is also involved in the pathogenesis of atopy and asthma. Similarly, JAK-STAT pathway inhibitors have been effective in the treatment of atopic dermatitis and asthma [14,15]. JAK-STAT pathway is also related with eosinophils, in our study the presence of eosinophils in histopathological examinations was associated with an increased probability of concomitant asthma. Further studies on this subject may contribute to the understanding of GA pathogenesis.

Regarding histopathology, GA comprises granulomatous inflammation in a palisading or interstitial pattern accompanied by mucin. A palisading pattern comprises a central zone containing necrobiotic collagen surrounded by palisadic histiocytes, while an interstitial pattern comprises histiocytes localized to the papillary or middle dermis distributed between collagen fibers and blood vessels [16]. There is a paucicellular appearance, with minimal mucin traces in the interstitial pattern [17].

In this study, histopathological examination of 21 patients was performed. The histopathological pattern was palisading in 6 patients, while the remaining (N = 15 patients) showed interstitial pattern. Trunk involvement was detected in 5 (33%) out of 15 patients with an interstitial pattern, but it was not detected in any patients with a palisadic pattern. Another striking finding was that all of the palisadic patterns were LGA, and 6 (40%) of those with an interstitial pattern showed GGA. The concomitant disease was present in 5 (33%) out of 15 patients with an interstitial pattern, whereas none of the patients with a palisadic pattern had concomitant disease. As a result, trunk involvement, GGA,
patterns of GA may indicate the possibility of different pathogenic mechanisms underlying these patterns. The palisading pattern may be induced by external factors, such as trauma or insect bites [1,18]. This may explain localized clinical involvement and a predilection for the extremities.

and accompanying diseases were detected in the interstitial pattern in a ratio of approximately 30%–40%, while these features were not present in the palisadic pattern.

The differences found between the involvement, distribution, and concomitant disease in interstitial and palisading patterns of GA may indicate the possibility of different pathogenic mechanisms underlying these patterns. The palisading pattern may be induced by external factors, such as trauma or insect bites [1,18]. This may explain localized clinical involvement and a predilection for the extremities.

**Table 2.** Descriptive statistics of histopathological features of pediatric granuloma annulare cases.

<table>
<thead>
<tr>
<th>Histopathological features</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>14</td>
<td>(73.7)</td>
</tr>
<tr>
<td>Hyperkeratosis, Acanthosis</td>
<td>1</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>1</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Orthokeratosis, Acanthosis</td>
<td>1</td>
<td>(5.3)</td>
</tr>
<tr>
<td>Pigmentation increase</td>
<td>2</td>
<td>(10.5)</td>
</tr>
<tr>
<td>Pattern of infiltrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial</td>
<td>15</td>
<td>(71.4)</td>
</tr>
<tr>
<td>Palisadic</td>
<td>6</td>
<td>(28.5)</td>
</tr>
<tr>
<td>Depth of infiltrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep dermis</td>
<td>3</td>
<td>(17.6)</td>
</tr>
<tr>
<td>Dermis</td>
<td>3</td>
<td>(17.6)</td>
</tr>
<tr>
<td>Medium</td>
<td>2</td>
<td>(11.7)</td>
</tr>
<tr>
<td>Middle and lower</td>
<td>1</td>
<td>(5.9)</td>
</tr>
<tr>
<td>Medium and deep</td>
<td>5</td>
<td>(29.4)</td>
</tr>
<tr>
<td>Upper and middle</td>
<td>2</td>
<td>(11.8)</td>
</tr>
<tr>
<td>Superficial and deep</td>
<td>1</td>
<td>(5.9)</td>
</tr>
<tr>
<td>Collagen degeneration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Present</td>
<td>21</td>
<td>(100.0)</td>
</tr>
<tr>
<td>Multinuclear giant cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>18</td>
<td>(90.0)</td>
</tr>
<tr>
<td>Present</td>
<td>2</td>
<td>(10.0)</td>
</tr>
<tr>
<td>Mucin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Present</td>
<td>17</td>
<td>(94.4)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>17</td>
<td>(80.9)</td>
</tr>
<tr>
<td>Present</td>
<td>4</td>
<td>(19.1)</td>
</tr>
<tr>
<td>Lymphohistiocytic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
<td>(9.5)</td>
</tr>
<tr>
<td>Present</td>
<td>19</td>
<td>(90.5)</td>
</tr>
</tbody>
</table>

**Figure 2.** (A) Palisading granuloma with a necrobiotic center in dense dermal infiltration (H&E,x100). (B) histiocye palisade around fragmented and partially granular collagen structures and sparse lymphocytes and karyorrhectic debris (H&E, x400).
Conversely, the concomitant disease ratio was higher in the interstitial pattern than in the palisadic pattern. Intrinsic stimuli in the immune system due to concomitant diseases may be related to the generalized clinical involvement and trunk localization detected in the interstitial pattern.

Pediatric GA cases can be followed-up without treatment. Topical corticosteroids are the most common option when treatment is preferred. In two previous studies on pediatric GA cases, most patients were managed without treatment, except for one case that received topical steroids. These studies observed complete regression in 92% of cases within the first two years [8,19]. In contrast, our study all patients received topical steroid treatment, and regression was observed in 86% of cases within a shorter timeframe (one year) compared to the previous literature. This difference in treatment approach and outcome may be related to the use of treatment in our study, compared to the management without treatment in the previous literature.

The etiology and pathogenesis of GA has not been clarified, and it is a clinical entity that requires further study. In pediatric GA cases, the data are even more limited than those for the adult population. This study contributes to the literature by reporting the presence of asthma in pediatric GA cases for the first time. The findings regarding histopathological involvement and clinical features may guide future studies. The limitations of the study are that it was conducted retrospectively (ie, there may be a lack of data), and the number of patients who underwent histopathology was relatively low.

In conclusion, atopy and asthma should be questioned in pediatric GA cases. There are differences between the involvement, distribution, concomitant disease, and histopathological patterns, which may indicate differences in pathogenesis.

### References


Clinical, Dermoscopic and Histopathological Evaluation of Basal Cell Carcinoma

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Key words: basal cell carcinoma, dermoscopy, dermatoscopy, subtype, pigmentation

Citation: Gürsel Ürün Y, Fiçicioğlu S, Can N. Clinical, Dermoscopic and Histopathological Evaluation of Basal Cell Carcinoma. Dermatol Pract Concept. 2023;13(1):e202304. DOI: https://doi.org/10.5826/dpc.1301a4

Accepted: September 9, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Dermoscopy aids in identifying histopathological subtypes and the presence of clinically undetectable pigmentation in basal cell carcinoma (BCC).

Objectives: To investigate the dermoscopic features of BCC subtypes and better understand non-classical dermoscopic patterns.

Methods: Clinical and histopathological findings were recorded by a dermatologist who was blinded to the dermoscopic images. Dermoscopic images were interpreted by two independent dermatologists blinded to the patients’ clinical and histopathologic diagnosis. Agreement between the two evaluators and with histopathological findings was evaluated using Cohen’s kappa coefficient analysis.

Results: The study included a total of 96 BCC patients with 6 histopathologic variants: nodular (n=48, 50%), infiltrative (n=14, 14.6%), mixed (n=11, 11.5%), superficial (n=10, 10.4%), basosquamous (n=10, 10.4%), and micronodular (n=3, 3.1%). Clinical and dermoscopic diagnosis of pigmented BCC showed high agreement with histopathological diagnosis. The most common dermoscopic findings according to subtype were as follows: nodular BCC: shiny white-red structureless background (85.4%), white structureless areas (75%), and arborizing vessels (70.7%); infiltrative BCC: shiny white-red structureless background (92.9%), white structureless areas (78.6%), arborizing vessels (71.4%); mixed BCC: shiny white-red structureless background (72.7%), white structureless areas (78.6%), arborizing vessels (71.4%); superficial BCC: shiny white-red structureless background (92.9%), white structureless areas (78.6%), arborizing vessels (71.4%); basosquamous BCC: shiny white-red structureless background (100%), short fine telangiectasias (54.4%); micronodular BCC: shiny white-red structureless background (100%), short fine telangiectasias (70%); basosquamous BCC: shiny white-red structureless background (100%), white structureless areas (80%), keratin masses (80%); micronodular BCC: short fine telangiectasias (100%).
Introduction

Basal cell carcinoma (BCC) is the most common skin cancer, and its incidence has doubled in the last 25 years [1, 2]. Although it rarely metastasizes, it is an important cause of morbidity in untreated patients [3]. BCC has diverse clinicopathological manifestations, including nodular, superficial, morpheaform, and pigmented variants [4]. BCCs are pigmented in more than 50% of dark-skinned people and less than 10% of light-skinned people [5, 6]. Knowledge of the histopathologic subtypes of BCC is important both for estimating the potential risk of recurrence and for choosing the type of treatment [7].

Dermoscopy is a noninvasive technique commonly used in the diagnosis of skin tumors [8]. This is an in vivo technique with 89-91.2% sensitivity and 95% specificity. BCC's dermoscopy includes features that vary with age, sex, race, histopathologic subtype, tumor location, and presence or absence of pigmentation [9]. When the dermoscopic features defined for superficial BCC are correctly determined, the rate of correct diagnosis increases to 99% [10]. There are no clear criteria for dermoscopic evaluation of rarer, aggressive histopathologic subtypes [6, 11, 12].

In this study, we aimed to establish a relationship between BCC histopathologic subtypes and the clinical and dermoscopic features of BCC, to describe the dermoscopic features of the rarer aggressive subtypes of BCC, to better understand the dermatoscopic patterns of nonvascular/nonpigmented structures to diagnose early BCC lesions before the classical pattern features are observed. Furthermore, our secondary purpose was to compare the frequency of clinical and dermoscopic pigmentation in patients with a histopathologic diagnosis of pigmented BCC.

Materials and Methods

This retrospective study was conducted in patients who presented to the dermatology and veneral diseases department of Trakya University between December 2017 and April 2021. The records of 96 patients with BCC who presented to the outpatient clinic between these dates were screened. Patients who had clinical and dermoscopic images on record, whose BCC subtype was determined histopathologically, and who had a histopathological diagnosis of total excision were included. The study was approved by the Trakya University Faculty of Medicine Ethics Committee (approval number: 10/18, date: 26.04.2021).

The main demographic features (age, sex, previous history of BCC, Fitzpatrick skin type, lesion location and whether it is in a sun-exposed or sun-protected area), clinical features (lesion palpability, ulceration, presence of pigmentation) were recorded for each patient by an independent dermatologist. The same dermatologist examined the patients’ clinical images and histopathologic data. Histopathologic assessment of pigmentation was based on the presence of pigmented basaloid sockets in the dermis or melanin deposits at the dermo-epidermal junction. The clinical diagnosis of hyperpigmentation was made by evaluating macro photographs and the retrospective history of the patients. Based on these findings, the patients were divided into two subgroups, clinically and histopathologically pigmented and nonpigmented BCC, and six subgroups based on histopathologic type.

Dermoscopic images were obtained with FotoFinder platform-based dermoscopy system (FotoFinder Systems GmbH, Germany) using 20X lenses. For each lesion, images were obtained in polarized mode using both contact and noncontact techniques. Minimal pressure was applied and ultrasound gel was used to preserve vessel morphology and ensure optimal visualization.

Dermoscopic images were interpreted on a computer display by two independent dermatologists who were both blinded to the patients’ clinical and histopathologic diagnosis. BCC and its subtypes were defined according to the criteria compiled by Reiter et al. [3]. Accordingly, structures were divided into three categories:

1. Pigmented structures: multiple blue-grey dots and globules, large blue-grey ovoid nests, leaflike areas, spoke-wheel areas, and concentric structures
2. Vascular structures: arborizing vessels, short fine telangiectasias, polymorphous vessels (more than one vessel pattern), and others (dotted, coiled [glomerular], looped [hairpin], and helical [corkscrew] vessels)
3. Nonvascular/nonpigmented structures: shiny white structures (shiny white streaks, shiny white blotches and strands, rosettes) surface changes (multiple small erosions, ulceration), shiny white-red structureless background.

In addition, the article by Kittler et al. [13] was used to standardize the naming of dermoscopic terms. The “rosettes”

Conclusions: In this study, arborizing vessels were the most common classical dermoscopic feature of BCC, while shiny white-red structureless background and white structureless areas were the most frequent non-classical dermoscopic features.
structure that Kittler et al. evaluated within the structure of shiny white structures was also examined in this subtitle. The dermoscopic diagnosis of basosquamous BCC was based on the study by Giacomel et al. [14]. In addition, some of the dermoscopic patterns indicating melanocytic lesions (brown to black dots/globules, blue/white veil, pigmented network, pseudopods, radial flowing, or a polymorphous vascular pattern) used by Altamura et al. were included in the evaluation [4].

In the dermoscopic evaluation, two dermatologists grouped the lesions as pigmented and non-pigmented according to the presence of at least one pigmentation-related dermoscopic criterion. These data were then compared with clinical and histopathologic grouping.

**Statistics**

Statistical analysis of the data was performed using IBM SPSS Statistics version 22 software. As the ages of the male and female patients were not normally distributed, Mann-Whitney U test was used to compare age between the groups. Cohen’s kappa coefficient was used to analyze agreement between the two evaluators and with histopathological findings. P values < 0.05 were considered statistically significant. Findings of milia-like cysts by the two independent dermatologists did not show statistically significant agreement with dermoscopic findings (p > 0.05). These dermoscopic features were excluded from the evaluation.

**Results**

The sociodemographic and clinical characteristics and dermoscopic images of a total of 96 patients with BCC were examined. The patients ranged in age from 32 to 87 years, with a mean age of 67.13 ± 12.58. Sixty-nine patients (71.9%) were men and 27 (28.1%) were women. Seventeen patients (17.7%) had a past history of BCC. The most common Fitzpatrick skin phototypes were II (42.7%) and III (42.7%).

Most tumors were located in the head and neck region (n = 87; 90.6%) and in sun-exposed areas (n = 78, 81.3%). On clinical evaluation, 35 (36.5%) of the lesions were flat, 32 (33.3%) were elevated, and 29 (30.2%) were nodular. Clinically visible ulceration and pigmentation were observed in 21 (21.9%) and 22 (22.9%) of the lesions, respectively (Table 1).

The following BCC histopathologic variants were observed: nodular (n = 48, 50%), infiltrative (n = 14, 14.6%); mixed (n = 11, 11.5%); superficial (n = 10, 10.4%); basosquamous (n = 10, 10.4%); and micronodular (n = 3.1%) (Table 1). The clinical images of the histopathologically confirmed BCC subtypes are shown in Figure 1.

The clinical characteristics of the histopathologic subtypes are compared in Table 2. The most common clinical appearance was nodular for nodular BCC (n = 20, 41.7%),

| Demographics, clinical and histopathological evaluation of basal cell carcinoma patients. |
|-----------------------------------------------|-----------------|
| **Age** | **N = 96** |
| **Mean ± SD** | 67.13 ± 12.58 |
| **Range** | 32.0-87.0 |
| **Sex [n (%)]** | |
| Male | 69 (71.9) |
| Female | 27 (28.1) |
| **Past history of BCC [n (%)]** | |
| Negative | 79 (82.3) |
| Positive | 17 (17.7) |
| **Skin phototypes [n (%)]** | |
| I | 3 (3.1) |
| II | 41 (42.7) |
| III | 41 (42.7) |
| IV | 10 (10.4) |
| V | 1 (1.0) |
| **Location [n (%)]** | |
| Head and neck | 87 (90.6) |
| Upper limbs | 3 (3.1) |
| Lower limbs | 1 (1.0) |
| Trunk | 5 (5.2) |
| **Site of the lesion [n (%)]** | |
| Sun exposed | 78 (81.3) |
| Sun protected | 18 (18.8) |
| **Palpability [n (%)]** | |
| Flat | 35 (36.5) |
| Elevated | 32 (33.3) |
| Nodular | 29 (30.2) |
| **Ulcer [n (%)]** | |
| Negative | 75 (78.1) |
| Positive | 21 (21.9) |
| **Clinical pigmentation [n (%)]** | |
| Non-pigmented | 74 (77.1) |
| Pigmented | 22 (22.9) |
| **Histopathological pigmentation [n (%)]** | |
| Non-pigmented | 66 (68.8) |
| Pigmented | 30 (31.3) |
| **Histopathological subtypes [n (%)]** | |
| Superficial | 10 (10.4) |
| Nodular | 48 (50) |
| Micronodular | 3 (3.1) |
| Infiltrative | 14 (14.6) |
| Mixed | 11 (11.5) |
| Basosquamous | 10 (10.4) |

BCC = Basal Cell Carcinoma.

* Histopathological pigmentation corresponds to pigmented basa-

lloid nests in the dermis or melanin deposition at the dermo-

epidermal junction.

The lesions’ pigmentation characteristics and their clinical,
dermoscopic, and histopathologic correlations were

elevated for infiltrative BCC (n=9, 64.3%), and flat for super-

ficial BCC (n=10, 100%).

The lesions’ pigmentation characteristics and their clinical,
Dermoscopic Characteristics of BCC Histopathologic Subtypes

Nodular BCC presented most commonly with shiny white-red structureless background (n = 41, 85.4%), shiny white blotches and strands (n = 36, 75%), arborizing vessels compared. According to this table, clinical and dermoscopic features were consistent with histopathological features in the diagnosis of pigmented BCC (Table 3).

The frequency of different dermoscopic features in BCC and its subtypes is detailed in Table 4.

Table 2. Clinical assessment of basal cell carcinoma subtypes.

<table>
<thead>
<tr>
<th></th>
<th>Nodular (n = 48)</th>
<th>Infiltrative (n = 14)</th>
<th>Mixed (n = 11)</th>
<th>Superficial (n = 10)</th>
<th>Basosquamous (n = 10)</th>
<th>Micronodular (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat</td>
<td>12 (25)</td>
<td>3 (21.4)</td>
<td>6 (54.5)</td>
<td>10 (100)</td>
<td>2 (20.0)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Elevated</td>
<td>16 (33.3)</td>
<td>9 (64.3)</td>
<td>1 (14.3)</td>
<td>0</td>
<td>4 (40.0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Nodular</td>
<td>20 (41.7)</td>
<td>2 (14.3)</td>
<td>1 (27.3)</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent percentages.

Table 3. Comparison of the presence of histopathologic pigmentation with the presence of clinical and dermoscopic pigmentation in basal cell carcinoma.

<table>
<thead>
<tr>
<th>Presence of clinical pigmentation</th>
<th>Negative</th>
<th>Positive</th>
<th>Total</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>k</td>
</tr>
<tr>
<td>Presence of clinical pigmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>64</td>
<td>97.0</td>
<td>10</td>
<td>33.3</td>
<td>74</td>
<td>77.1</td>
<td>0.686</td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>3.0</td>
<td>20</td>
<td>66.7</td>
<td>22</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Presence of dermoscopic pigmentation</td>
<td>63</td>
<td>95.5</td>
<td></td>
<td></td>
<td>63</td>
<td>65.6</td>
<td>0.929</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>4.5</td>
<td>30</td>
<td>100.0</td>
<td>33</td>
<td>34.4</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 96</td>
<td>66</td>
<td>68.8</td>
<td>30</td>
<td>31.3</td>
<td>96</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Cohen's kappa concordance test (k)

Dermoscopic Characteristics of BCC Histopathologic Subtypes

Nodular BCC presented most commonly with shiny white-red structureless background (n = 41, 85.4%), shiny white blotches and strands (n = 36, 75%), arborizing vessels...
Table 4. Distribution of dermatoscopic patterns according to different types of basal cell carcinoma.

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<tr>
<th>Vascular structures</th>
<th>Nodular n (%)</th>
<th>Infiltrative n (%)</th>
<th>Mixed n (%)</th>
<th>SF n (%)</th>
<th>BS n (%)</th>
<th>MN n (%)</th>
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<td>Short fine telangiectasias</td>
<td>17 (35.4)</td>
<td>8 (57.1)</td>
<td>6 (54.5)</td>
<td>7 (70)</td>
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<th>Pigmented structures</th>
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SF = Superficial; BS = Basosquamous; MN = Micronodular; BCC = Basal Cell Carcinoma.

(n = 34, 70.7%), and ulceration (n = 28, 58.3%). When pigmentation was present, the most common structure was large blue-grey ovoid nests (n = 13, 27.1%).

The most common dermoscopic findings in infiltrative BCC were shiny white-red structureless background (n = 13, 92.9%), shiny white blotches and strands (n = 11, 78.6%), arborizing vessels (n = 10, 71.4%), ulceration (n = 10, 71.4%), and short fine telangiectasias (n = 8, 57.1%).

In mixed BCC, the most common dermoscopic findings were shiny white-red structureless background (n = 8, 72.7%), shiny white blotches and strands (n = 6, 54.4%), and short fine telangiectasias (n = 6, 54.4%).

The most common dermoscopic findings in superficial BCC were shiny white-red structureless background (n = 10, 100%), short fine telangiectasias (n = 7, 70%), shiny white blotches and strands (n = 6, 60%), and multiple small erosions (n = 6, 60%).

Basosquamous BCC presented with dermoscopic findings of shiny white-red structureless background (n = 10, 100%), shiny white blotches and strands (n = 8, 80%), keratin masses (n = 8, 80%), arborizing vessels (n = 7, 70%), and polymorphous vessels (n = 6, 60%).

In micronodular BCC, short fine telangiectasias were observed on dermoscopy (n = 3, 100%). In the presence of pigmentation, the most common dermoscopic finding was brown globules (n = 3, 100%).

Various dermoscopic images of basal cell carcinomas with vascular structures, pigmented structures, shiny white structures, surface changes, shiny white-red structureless background, blue-whitish veil, and keratin masses were shown in detail in Figure 2-5.

Discussion

In this study, patients with clinical and dermoscopic pigmented/unpigmented BCC were evaluated using polarized dermoscopy to assist in the diagnosis of BCC subtypes.

The sociodemographic characteristics of the patients in our study were found to be consistent with previous studies [11, 15]. In various publications, nodular BCC has
consistently been reported as the most common subtype (57.6-78.7%), followed by superficial BCC (14.8-17.5%) and infiltrative BCC (6.2-26.2%) [16,17]. Arits et al. reported total rates for superficial and infiltrative BCC of 23.8% and 27.6%, respectively [18]. In our study, infiltrative BCC was more frequent than superficial BCC.

When BCC subtypes were clinically evaluated, our results were similar to those of Lallas et al. [19]. A notable feature of both studies was the absence of nodular lesions among superficial BCCs. Superficial BCCs classically present as a well-circumscribed and erythematous thin plaque or patch with scale [20]. Both Lallas et al. and our studies support this clinical appearance. Micronodular BCC is difficult to distinguish clinically from superficial and nodular BCC and can present as erythematous macules or thin papules/plaques [20]. The clinically rare nodule appearance of micronodular BCC was observed both in our study and by Lallas et al. [19].

In the review by Reiter et al., shiny white structures and shiny white-red structureless background structures were evaluated in nonvascular/nonpigmented structures. It has been emphasized that different terms were used in each study [3]. In studies conducted in 2005 and 2008, the term “shiny white-red structureless” was used, and these structures were observed in all superficial BCCs [21, 22]. Trigoni et al. included shiny white-red structureless background features observed within lesions under a general description of white-red structureless areas [23]. Emiroglu et al., on the other hand, referred to these structures as “milky-pink to red background” and emphasized that they are also seen in other BCC subtypes that are mostly superficial [24]. A 2021 publication used this term as “red-white homogenous areas” and noted that they are present in superficial and nodular BCC subtypes [25]. We evaluated the lesions similar to the statement by Trigoni et al. Accordingly, in our study, the shiny white-red structureless background was found in all superficial BCC cases as well as in other BCC subtypes. Since this is a nonvascular/nonpigmented structure, a dermoscopic feature in BCC diagnosis, it was not considered in some studies [26, 27]. The main problem is that the studies did not use a standardized term. We believe that standardization is needed in defining nonvascular/nonpigmented structures.

There are few studies in the literature comparing the incidence of shiny white structures in BCC subtypes [24, 26].
When these studies and our study are examined, shiny white structures are most common in the nodular BCC subtype. When the incidence of rosette structures in BCC subtypes is examined, they were most commonly seen in superficial BCCs in the study by Suppa et al. [26], whereas they were most commonly seen in nodular BCCs in our study. A better understanding of these structures will facilitate the diagnosis of BCC subtypes.

Lallas et al. reported that pigmentation could be detected in 30% of clinically nonpigmented BCCs using dermoscopy and emphasized that dermoscopy has the potential to reveal clinically undetectable pigmentation [28]. In our study, there was consistency among clinical (22.9%), dermoscopic (34.4%), and histopathological (31.3%) features in diagnosing pigmented BCC. As in the study of Lallas et al., the frequency of clinically pigmented BCC was lower than the rate of dermoscopic and histopathological diagnosis, but the difference was not statistically significant [28]. This may be due to the small sample size.

Pigmented BCC is considered a low-risk variant in some publications [29]. However, Xavier-Júnior et al. described pigmented BCCs with higher risk morphology, including sclerosing and micronodular subtypes [30]. Lallas et al. emphasized that pigmentation can occur in all subtypes [28]. We also observed dermoscopic pigmentation findings in all subtypes, most commonly in nodular BCC.

Altamura et al. reported that 40.6% of BCCs had dermoscopic findings suggestive of the features of melanocytic lesions [4]. In our study, polymorphous vascular pattern was observed in 36 patients (37.5%), brown globules in 18 patients (18.8%), dots in 13 patients (13.5%), and blue-whitish veil in 6 patients (6.3%). Altamura et al. emphasized that these dermoscopic features may make it difficult to distinguish pigmented (especially heavily pigmented) BCCs from others.

Figure 3. The different dermoscopic pigmentation patterns of basal cell carcinoma. (A) Multiple blue-grey dots, (B-C) Multiple blue-grey globules, Large blue-grey ovoid nests, (D) Brown dots, (E) Brown globules, (F) Brown nets, (G) Concentric structures, (H) Leaflike areas.
melanocytic nevi and melanomas [4]. Clinician caution is advised in this respect.

Infiltrative BCC was reported to present with arborizing vessels (76%), followed by ulceration (44%) and short fine telangiectasias (40%) [3, 31]. The dermoscopy study conducted by Popadić included three infiltrative BCCs and white shiny areas were detected in all of these patients [32]. Information about the subgroups of white shiny areas was
not given in this study. Pampena et al. evaluated 71 infiltrative BCC patients and reported the most common dermoscopic findings to be short white streaks (77.5%), arborizing vessels (71.8%), and shiny red-white structureless areas (69.0%) [33]. Of the white shiny areas in our study, the most common were shiny white blotches and strands (78.6%) and shiny white streaks (42.9%). In infiltrative BCCs, knowledge of the subgroups of shiny white structures will help in diagnosis.

Pampena et al. determined that short fine telangiectasias are common on dermoscopy of infiltrative BCC and concluded that arborizing vessels and short fine telangiectasias can be seen in the same lesion [33]. Similarly, we observed both arborizing vessels (71.4%) and short fine telangiectasias (57.1%) in our infiltrative BCC patients. When the same authors evaluated the degree of dermoscopic pigmentation in infiltrative BCC, they found that these lesions were more amelanotic and less pigmented than nodular BCC [33]. In our study, the frequency of pigmentation seen in infiltrative BCC (61.1%) and mixed BCC (61.1%) patients was lower than in other BCC subtypes.

Reiter et al. in their review reported that the most common dermoscopic findings seen in superficial BCC were short fine telangiectasia (60%), multiple small erosions (43%), and shiny white structures (43%). Furthermore, 79% of lesions were observed to have a white-red structured background. They emphasized that shiny white-red structureless background is a unique dermoscopic finding for superficial BCC [3]. Papageorgiou et al. emphasize that the white shiny blotches/strands structure is a predictor of superficial BCC in anatomic sites other than the lower extremities [34]. In our study, shiny white-red structureless background and shiny white blotches and strands structures are the most common nonvascular/nonpigmented structures in superficial BCC, which is consistent with previous literature. Zalaudek et al. accepted blue-gray ovoid nests as a negative predictor of superficial BCC [35]. Similarly, blue-gray ovoid nests were not detected in any of the superficial BCCs in our study. Considering that brown structures are associated with melanin, accumulation is observed in the dermo-epidermal junction on dermoscopy and constitutes a feature of superficial BCC [28]. In light of available data, brown dots and globular structures were mostly seen in superficial and micronodular BCC in our study.

Verduzco-Martínez et al. evaluated the dermoscopic findings of a patient with micronodular BCC and observed truncated vessels and globules [36]. In their study evaluating the dermoscopic properties of aggressive BCC types including micronodular BCC, Kim et al. reported that the appearance of multiple blue-gray globules was more common [37]. El-Sayed et al. observed arborizing vessels and blue-gray globules in a patient with micronodular BCC [11]. Our findings are consistent with the study by Verduzco-Martínez et al. [36]. However, the insufficient number of patients in all studies makes it difficult to comment on the specific findings of micronodular BCC.

In patients with basosquamous BCC, Giacomel et al. observed dermoscopic features of unfocused (peripheral) arborizing vessels (73%), keratin masses (73%), shiny white blotches and strands (73%), ulceration or blood crusts (68%), polymorphous vessels (50%) [14]. Akay et al. reported dermoscopic features of keratin mass (91.7%), ulceration (69.4%), shiny white blotches and strands (69.4%), and polymorphous vessels (61.1%) in basosquamous BCC [38]. When the results of these two studies and our own are evaluated, keratin masses, shiny white blotches and strands, ulceration, and polymorphous vessels are among the most common dermoscopic findings. Dermoscopy of basosquamous BCC shows features of keratinization with vascular patterns suggestive of BCC [38]. The greatest limitation of our study was that arborizing vessel structures were not grouped as focused or unfocused when evaluating basosquamous BCC. Therefore, we are unable to evaluate the appearance of arborizing vessels in this group.

This study has several limitations. Firstly, it was retrospective and conducted in a small patient population. In addition, the population living in the Trakya area is predominantly Fitzpatrick skin type II-III. Another limitation is that histopathologic examinations were conducted by a single pathologist who was not blinded. Finally, the absence of a control group (dermoscopic images including benign and malignant lesions) was another limitation.

**Conclusion**

In this study, the most common finding among the classical dermoscopic features of BCC was arborizing vessels, while shiny white-red structureless background and shiny white blotches and strands were the most frequent nonvascular/nonpigmented structures dermoscopic features. The dermoscopic features observed in the BCC histopathologic subtypes were consistent with the literature. However, a specific/dermoscopic structure belonging to BCC subtypes could not be detected. Of the less common subtypes, the frequency of short fine telangiectasias was 100% in micronodular BCC, whereas shiny white-red structureless background was detected in 100%, shiny white blotches and strands in 80%, and keratin mass in 80% of basosquamous BCCs. The small number of these subtypes in our population and the absence of the morpheaform type precludes a comprehensive interpretation of dermoscopic presentations in all BCC subtypes. Further studies are needed for this purpose.


Mortality of Malignant Melanoma in Central Serbia, in the Period 1999-2015

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Key words: malignant melanoma, mortality, risk factors, Serbia


Accepted: June 20, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Malignant melanoma is one of the rarest forms of skin cancer but it is the most deadly.

Objective: The objective of this paper was to analyze the epidemiological characteristics and trends of mortality from malignant melanoma in the population of Central Serbia in the period 1999-2015.

Methods: The study was designed as a retrospective descriptive epidemiological study. Standardized mortality rates were used in statistical data processing. A linear trend model and regression analysis were used to examine trends in malignant melanoma mortality.

Results: In Serbia, malignant melanoma mortality shows an increasing trend. The overall age-adjusted melanoma death rate was 2.6 per 100,000 with a higher death rate among men (3.03 per 100,000) than among women (2.1 per 100,000). Malignant melanoma mortality rates increase with age in both sexes and are highest in the age group of 75 and older. The highest increase in mortality in men is recorded in the 65-69 age group, with an average percentage increase of 21.33 (95% CI, 8.40 - 51.05), while in women the largest increase in mortality was recorded in the 35-39 age group, with an average percentage increase of 31.4 and in the 70-74 age group, 12.9.

Conclusions: The trend of increasing mortality from malignant melanoma in Serbia is similar to those in most developed countries. Education and improvement of awareness in the general population and among health professionals are vital to reducing melanoma mortality in the future.
Introduction

Malignant melanoma accounts for 4% of all skin cancers and 1.7% of all cancers [1]. Although it still accounts for less than 5% of all skin malignancies, melanoma causes about 80% of skin cancer deaths [2]. The incidence of cutaneous melanoma has increased sharply in recent years in all parts of the world, with a steady increase in incidence among the white population, while the mortality associated with it remains stable [3-5]. It should also be noted that the incidence of melanoma has increased due to better education and improvement of awareness among patients and due to the development of dermoscopy [6].

According to Globocan data from 2018, the total number of deaths from malignant melanoma in the world was 60,712, which ranks it 22nd in the structure of mortality from malignant tumors of all localization [7]. Mortality rates in different populations of the world multiple vary depending on the level of development, so mortality is almost 5 times higher in developed countries than in developing countries [8,9]. Worldwide, the highest mortality rates are registered in regions such as North America, Northern Europe, Australia and New Zealand, while lower rates are commonly found in South American and African countries. For 2018, global data on skin melanoma revealed age-standardized mortality rates of approximately 0.63 deaths per 100,000 inhabitants (0.78 deaths per 100,000 inhabitants for men and 0.50 for women) [7].

Epidemiological studies show that melanoma is more common in older adults than in younger people and is more common in men than in women, but the ratio of these rates between the sexes varies with age [10, 11]. For example, the incidence rate is three times higher in men aged 80 and older than in women of the same age [12]. Although the incidence of melanoma is lower in people under the age of 40, it is one of the most common cancers diagnosed among adolescents and young adults [13].

Although the etiology of melanoma has not been fully elucidated, the findings of studies indicate the importance of the interaction between genetic, biological, and environmental factors. Several meta-analyses have identified key risk factors such as: family history of melanoma, age, history of sunburn and exposure to ultraviolet (UV) radiation, fair-skinned people, increased number of nevi, dysplastic nevi, genetic factors (CDKN2A, CDK4, MC1R genes, TYRPI) [14,15]. The most important and potentially modifying environmental risk factor for the development of malignant melanoma is exposure to ultraviolet (UV) rays due to their genotoxic effects [10,16,17].

According to the latest IARC estimations (2018), the estimated mortality rate in Serbia is 2.5 / 100,000 inhabitants [18]. Compared to other countries, although Serbia has lower mortality rates than the highest estimated in the world, it is in the group of countries with a higher risk of disease. Unless additional efforts in prevention are made, the number of melanoma cases is projected to increase in Serbia over the next 15 years, with a concomitant increase in healthcare costs.

The aim of the research is to analyze the epidemiological characteristics and trends of mortality from malignant melanoma in the population of Central Serbia in the period 1999-2015.

Materials and Methods

The study was designed as a retrospective descriptive epidemiological study. The research used data from the Cancer Registry of Central Serbia, formed on the basis of reports of malignant diseases for the period 1999-2015. The Population Register for Cancer was established in Serbia in 1970 and since 1998, the Cancer Registry of Central Serbia has been admitted to the International (IACR) and European Association of Cancer Registries (ENCRA). In the registers, due to numerous data sources and the need for their verification and analysis, the usual time period for data collection is two years, after which the report is published, which is the reason why the last published data from 2015 will be used.

Standardized mortality rates were used in statistical data processing. Mortality rates were calculated based on data on deaths from malignant melanoma in the Cancer Registry of Central Serbia. All reported melanoma deaths were coded according to the International Classification of Disease, 10th Revision (code S43.0). The cases were grouped by gender into 5-year age groups. The size and composition of the population by age and sex were obtained by the 1991, 2002, and 2011 Censuses. The population of Central Serbia by age and sex in the years between the Censuses were estimated based on natural increase and migration.

Age-adjusted mortality rates were calculated by direct standardization, using the world’s population and presented per 100,000 inhabitants. A linear trend model and regression analysis were used to examine trends in malignant melanoma mortality. The percentage of the change in the mortality rate was calculated as the percentage of the difference between the adjusted rates for two consecutive years, and then as the average value of these changes over the entire observation period. Confidence intervals (CI) for average age-adjusted and age-specific mortality rates were estimated with 95% probability. Bilateral P values have been reported and are considered to show statistical significance if they are lesser than 0.05. Data were processed using the statistical package for social sciences, version 19.0 (SPSS Inc., Chicago, IL, USA).
Results

In 2015, a total of 195 melanoma deaths occurred in Central Serbia, which constitutes 1.3% of the total number of cancer deaths and ranks 17th in the structure of cancer mortality of all localizations. During the 17-year observation period, there was a significant decrease in the total mortality of the population (y = -8.7001x + 582.67; p = 0.001; % change = - 8.83) (Figure 1), with a significant increase in mortality from all malignant tumors in total (y = 0.6343x + 115.13; p = 0.004; % change = + 0.27) and in both sexes (Figure 2).

In the same period, mortality from malignant melanoma recorded an increasing trend (y = 0.0194x + 1.3682; p = 0.009; % change = + 1.94). Observed by gender, there is a significant trend of increasing mortality in men (y = 0.0486x + 1.5494; p = 0.036; % change = + 6.26), while in women there is a trend of declining mortality from malignant melanoma (y = -0.0124x + 1.3282; p = 0.088; % change = + 0.43). (Figure 3).

The overall age-adjusted melanoma death rate was 2.6 per 100,000, with a higher death rate among men (3.03 per 100,000) than among women (2.1 per 100,000).

Malignant melanoma mortality rates increase with age in both sexes and are highest in the age group of 75 and older (10.15 per 100,000 for men; 8.32 per 100,000 for women) (Table 1). Low mortality rates have been reported in men and women under the age of 30. The largest increase in mortality in men was recorded in the 65-69 age group, with an average percentage increase of 21.33 (95% CI, 8.40 - 51.05), while in women there is a trend of declining mortality from malignant melanoma (y = -0.0124x + 1.3282; p = 0.088; % change = + 0.43). (Figure 3).

In terms of the global distribution of malignant melanoma, the standardized malignant melanoma mortality rate expressed on 100,000 inhabitants is higher for men than for women in all regions of the world: Australia and New Zealand (men 5.9; women 2.4); Northern Europe (men 2.5; women 1.6), North America (men 2.6; women 1.2), Western Europe (men 2; women 1.3). Less significant differences in mortality rates are present in less developed regions of the Caribbean (men 0.3, women 0.2), West Africa (men 0.5; women 0.3); East Asia (men 0.4; women 0.3); Southeast Asia (men 0.3; women 0.2); North Africa (men 0.2; women 0.2), Central Asia (men 0.2; women 0.1) [7].

The results of our study showed that mortality from malignant melanoma is higher in men than in women, which is in line with most published studies [11, 23]. The average standardized mortality rate for men in the world was 0.78 per 100,000 in 2018, and 0.50 per 100,000 for women in 2018. In terms of the global distribution of malignant melanoma, the standardized malignant melanoma mortality rate expressed on 100,000 inhabitants is higher for men than for women in all regions of the world: Australia and New Zealand (men 5.9; women 2.4); Northern Europe (men 2.5; women 1.6), North America (men 2.6; women 1.2), Western Europe (men 2; women 1.3). Less significant differences in mortality rates are present in less developed regions of the Caribbean (men 0.3, women 0.2), West Africa (men 0.5; women 0.3); East Asia (men 0.4; women 0.3); Southeast Asia (men 0.3; women 0.2); North Africa (men 0.2; women 0.2), Central Asia (men 0.2; women 0.1) [7].

In Europe, the standardized mortality rate of malignant melanoma for men is 3.2 per 100,000, and for women 1.9 per 100,000, with differences varying between regions of Europe: Western Europe (3.3 men and 1.9 women) in Central and Eastern Europe (3.0 and 2.0) in Northern Europe.

Discussion

Mortality from malignant melanoma in Serbia records an upward trend and mortality rates for malignant melanoma in Serbia remain among the highest in the world. Similar trends are being observed around the world despite numerous efforts to improve primary prevention and early detection, and these increasing rates are affecting public health and the economic burden of the disease [11, 19]. Melanoma mortality rates have increased marginally among fair-skinned populations. Mortality rates are highest in Australia and New Zealand (3.4 per 100,000) and Northern Europe (2.0 per 100,000), while the lowest rates are recorded in South Central Asia and Eastern Asia (0.19) [7].

Trends in melanoma mortality are variable and are affected by latitude, ethnicity, age, and gender [20-22]. In high-risk regions, the mortality rate increased historically until the 1980s, peaking between 1988 and 1990, and then gradually maintained a slow increase. Over the last decade, the death rate has been growing steadily by 1.5% in the most of observed countries, such as New Zealand and Australia [10].

Mortality rates in northern European countries (Norway, Sweden, Netherlands) are among the highest in the world. Thus, according to the latest data from Globocan, in Norway in 2018, the total number of deaths from malignant melanoma was 13.2% of cancer of all localizations, which ranks it 7th in the structure of cancer mortality of all localizations. For the same period, in Sweden, the number of deaths from malignant melanoma accounted for 2.4% of cancer deaths of all localizations, which ranks it 12th, the standardized mortality rate is 2.5 per 100,000 inhabitants. The total number of deaths from malignant melanoma in the Netherlands in 2018 presents 2.0%, of deaths from cancer of all localizations, which ranks it 17th in the structure of cancer mortality of all localizations [7].

Differences in skin type, length, and sun exposure patterns may partly explain the lowest mortality rates recorded in some Middle Eastern countries (Qatar 0.04 per 100,000 inhabitants, Saudi Arabia 0.10 per 100,000 inhabitants, and Yemen 0.11 per 100,000 inhabitants), Africa (Egypt 0.13 per 100,000 inhabitants; Libya 0.14 per 100,000 inhabitants; Asian countries (India - 0.16 per 100,000 inhabitants, China - 0.18 per 100,000 inhabitants and Vietnam 0.08 per 100,000 inhabitants), some Central American countries (Barbados 0.0 per 100,000 inhabitants and Haiti 0.16 per 100,000 inhabitants) and Europe (Albania 0.53 per 100,000 inhabitants; Montenegro 0.89 per 100,000 inhabitants) [18].

The results of our study showed that mortality from malignant melanoma is higher in men than in women, which is in line with most published studies [11, 23]. The average standardized mortality rate for men in the world was 0.78 per 100,000 in 2018, and 0.50 per 100,000 for women in 2018. In terms of the global distribution of malignant melanoma, the standardized malignant melanoma mortality rate expressed on 100,000 inhabitants is higher for men than for women in all regions of the world: Australia and New Zealand (men 5.9; women 2.4); Northern Europe (men 2.5; women 1.6), North America (men 2.6; women 1.2), Western Europe (men 2; women 1.3). Less significant differences in mortality rates are present in less developed regions of the Caribbean (men 0.3, women 0.2), West Africa (men 0.5; women 0.3); East Asia (men 0.4; women 0.3); Southeast Asia (men 0.3; women 0.2); North Africa (men 0.2; women 0.2), Central Asia (men 0.2; women 0.1) [7].

In Europe, the standardized mortality rate of malignant melanoma for men is 3.2 per 100,000, and for women 1.9 per 100,000, with differences varying between regions of Europe: Western Europe (3.3 men and 1.9 women) in Central and Eastern Europe (3.0 and 2.0) in Northern Europe.
Men are approximately 1.5 times more likely to develop melanoma than women. The incidence of melanoma is higher in women than in men until they reach the age of 40, however, from the age of 75, the incidence is almost three times higher in men than in women [25]. Mortality from melanoma is the lowest in Albania (0.8 and 0.6 per 100,000 inhabitants), Montenegro (1.2 and 1.3 per 100,000 inhabitants), Romania (1.9 and 1.4 per 100,000 inhabitants), Spain (1.9 and 1.3 per 100,000 inhabitants). On the other hand, the highest values for men and women are in Croatia (4.6 and 2.5 per 100,000 inhabitants), North Macedonia (4.0 and 2.2 per 100,000 inhabitants), Slovenia (4.8 and 3.2 per 100,000 inhabitants), Poland (4.0 and 2.4 per 100,000 inhabitants), Slovakia (4.8 and 3.2 per 100,000 inhabitants), Finland (4.4 and 1.7 per 100,000 inhabitants), Norway (6.3 and 4.1 per 100,000 inhabitants) and the Netherlands (4.6 and 3.1 per 100,000 inhabitants) [24].

Men are approximately 1.5 times more likely to develop melanoma than women. The incidence of melanoma is higher in women than in men until they reach the age of 40, however, from the age of 75, the incidence is almost three times higher in men than in women [25]. Mortality from melanoma is the lowest in Albania (0.8 and 0.6 per 100,000 inhabitants), Montenegro (1.2 and 1.3 per 100,000 inhabitants), Romania (1.9 and 1.4 per 100,000 inhabitants), Spain (1.9 and 1.3 per 100,000 inhabitants). On the other hand, the highest values for men and women are in Croatia (4.6 and 2.5 per 100,000 inhabitants), North Macedonia (4.0 and 2.2 per 100,000 inhabitants), Slovenia (4.8 and 3.2 per 100,000 inhabitants), Poland (4.0 and 2.4 per 100,000 inhabitants), Slovakia (4.8 and 3.2 per 100,000 inhabitants), Finland (4.4 and 1.7 per 100,000 inhabitants), Norway (6.3 and 4.1 per 100,000 inhabitants) and the Netherlands (4.6 and 3.1 per 100,000 inhabitants) [24].

### Table 1. The average age-specific mortality rates and linear trend of Melanoma malignum in Central Serbia, in 1999–2015.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Age-specific rates* (per 100,000)</th>
<th>Linear trend</th>
<th>R2</th>
<th>p</th>
<th>Average annual percentage change (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
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<td>0-4</td>
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<td>15-19</td>
<td>0.00</td>
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<tr>
<td>20-24</td>
<td>0.27</td>
<td>†</td>
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<tr>
<td>25-29</td>
<td>0.42</td>
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<td>1.69</td>
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<td>40-44</td>
<td>2.03</td>
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<td>45-49</td>
<td>3.33</td>
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<td>55-59</td>
<td>7.99</td>
<td>†</td>
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<tr>
<td>60-64</td>
<td>4.15</td>
<td>y = 5.26 + 0.21·x</td>
<td>0.274</td>
<td>0.031</td>
<td>7.93 (-9.16 – 24.97)</td>
</tr>
<tr>
<td>65-69</td>
<td>4.85</td>
<td>y = 5.87 + 0.46·x</td>
<td>0.321</td>
<td>0.018</td>
<td>21.33 (-8.40 – 51.05)</td>
</tr>
<tr>
<td>70-74</td>
<td>7.68</td>
<td>y = -6.23 +0.56·x</td>
<td>0.620</td>
<td>&lt; 0.0005</td>
<td>10.84 (-8.73 – 30.41)</td>
</tr>
<tr>
<td>75+</td>
<td>10.15</td>
<td>y = 7.16 + 0.83·x</td>
<td>0.669</td>
<td>&lt; 0.0005</td>
<td>10.96 (-9.59 – 31.51)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
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<td>30-34</td>
<td>0.88</td>
<td>†</td>
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<tr>
<td>35-39</td>
<td>1.48</td>
<td>y = 2.28 - 0.10·x</td>
<td>0.273</td>
<td>0.032</td>
<td>31.41 (-23,10 – 85.91)</td>
</tr>
<tr>
<td>40-44</td>
<td>1.80</td>
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<td>45-49</td>
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<td>65-69</td>
<td>3.42</td>
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<tr>
<td>70-74</td>
<td>5.42</td>
<td>y = 2.90 + 0.32·x</td>
<td>0.430</td>
<td>0.004</td>
<td>12.86 (-14.41 – 40.14)</td>
</tr>
<tr>
<td>75+</td>
<td>8.32</td>
<td>†</td>
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</table>
When age is taken into account, adolescents and young adult women are more susceptible to melanoma than men [20]. This could be partly due to the widespread use of tanning beds among women, which is associated with an increased risk of melanoma [11]. However, after the age of 40, the incidence rate of melanoma among men is higher than among women [25]. Some believe that this increased sensitivity in men may be partly influenced by androgens [26].

Malignant melanoma begins to rise sharply in men aged 40-44 and is especially high in those over 60 years of age. In women, a sharp increase was also observed at the age of 40-44, while the rate is especially high between the ages of 55 and 59. In some countries, the increase in the standardized mortality rate for those over the age of 85 is twenty times higher than for those at the age of 40-44 (Australia 42.65 per 100,000 and 2.62 per 100,000) [18].

**Figure 1.** Trends of age-adjusted mortality rates for all causes of death, all malignant tumors and malignant melanoma in Central Serbia in the period 1999-2015.

**Figure 2.** Trends of age-adjusted mortality rates all malignant tumors in Central Serbia by sex, in the period 1999-2015.
Higher survival rates in women are also attributed to biological differences such as oxidative stress response, sex hormones or vitamin D metabolism and other influencing factors that have yet to be explored [27]. Speculation about the link between steroid hormones and melanoma arose when population studies found that women had a higher survival rate than men, which was evident between 1973 and 1997 when men had a death rate from melanoma that was twice as high as in women [28]. Furthermore, the history of malignant melanoma in women is rare before puberty and then increases sharply during the reproductive period and decreases during the menopausal years, which implies the involvement of estrogen. This phenomenon has led to the suggestion that hormones play an important role in melanoma. However, the results of epidemiological studies that assess the risk of melanoma in relation to hormonal and reproductive factors, such as the use of oral contraceptives, pregnancy and menopause, are contradictory; some studies did not show a cause-and-effect relationship, while others found an increased risk of melanoma [26,29]. Thus, the existence of a link between hormones and melanoma remains uncertain.

Other authors believe that these gender differences may be partly due to low rates of sun protection and more time spent outdoors during life compared to women. In addition, men are less likely to use sunscreen compared to women and are less aware of the importance of preventive measures, so melanoma is usually detected when the disease is present at an advanced stage, while women are more willing to seek medical help earlier and thus to detect changes in the earlier stage of the disease [5].

Many authors state that melanoma is more common in the elderly [30,31]. The results of our study also confirmed that age is a significant risk factor for malignant melanoma. Mortality rates are highest in people aged 75 and older in both sexes, with the highest percentage increase in mortality recorded in the 35-39 age group in women, and in the oldest age groups in men (65-69, 70-74, and 75 and older).

Similar to our results, a study conducted by Karimkhani et al found that malignant melanoma mortality rates are highest in the 75-79, 70-74, and 80 and older age groups [30]. In America, the percentage share of individual age groups in the total number of deaths shows the highest percentage (23.9%) in the 75-84 age group [32].

Older adults have more cumulative sun exposure than younger ones, and each additional decade of intense sun exposure increases the risk of melanoma [33,34]. The results of epidemiological research show that high sun exposure in the first 10 years of life more than doubles the risk of melanoma, while intense, occasional sun exposure during each decade until the age of 29 increases the risk of melanoma by more than 1.5 times [35]. More than five sunburns double the risk of melanoma for both those under 15 and those over 15 years of age. However, other studies have found that the number of sunburns before the age of 30 significantly increased the risk of melanoma, and the positive connection with the risk of melanoma is weaker in burns that occurred in those older than 30 years [36].
Conclusion

The trend of increasing mortality from malignant melanoma in Serbia is similar to those in most developed countries. Due to the high incidence of malignancies and their high mortality rates, the prevention of malignant diseases has a huge public health potential and represents the most effective approach to the control of malignant diseases. Given the strong and continuous trend of demographic aging and the growing burden of the disease, it is estimated that a significant number of new cases of melanoma could be prevented by implementing effective prevention measures ranging from primary, targeted to reducing outdoor and indoor sunbathing exposure in order to reduce the exposure to ultraviolet (UV) radiation, to secondary methods of prevention such as whole-body visual examinations of the skin. Education and improvement of awareness in the general population and among health professionals are vital to reducing melanoma mortality in the future.

The results of this research can be used as a starting point in creating strategies at the community level, as well as for the development of prevention programs aimed at vulnerable and high-risk categories of the population such as children, adolescents and their parents, which would significantly reduce health care costs and total disease burden.

References


Clinical Efficacy of Medical Dextrose Tincture Liquid in the Treatment of Facial Photoaging

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Key words: medical dextran tincture liquid, facial photoaging, clinical efficacy


Accepted: May 5, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Exogenous aging mainly refers to photo-aging, which is caused by environmental factors including ultraviolet exposure. Dextran is a homopolysaccharide composed of glucose as monosaccharide, and glucose units are connected by glycosidic bonds.

Objectives: The purpose of this study was to explore the clinical efficacy of medical dextrose tincture liquid (medical dextrose tincture) in the treatment of facial photoaging.

Methods: Thirty-four volunteers were included in the randomized double-blind study. According to the random number table method, the subjects were randomized into control and treatment groups. The subjects in the control and treatment groups were treated with medical hyaluronic acid gel and medical dextrose tincture, respectively. They received mesotherapy therapy three times with an interval of 28 days between treatments. Video image acquisition was performed before treatment and 28 days after treatment. Skin moisture content, glossiness, heme content, collagen density, and elasticity were tested. The subjective evaluations of subjects and doctors before and after treatment were compared.

Results: Compared with the pre-treatment baseline, medical dextran tincture significantly increased skin moisture retention, skin gloss, and skin collagen density (p<0.001). Additionally, the skin retraction time was significantly reduced, and the skin retraction time was also markedly decreased after treatment with medical dextran tincture (p<0.001). The effects of medical dextran tincture were more significant in comparison with medical hyaluronic acid gel (p<0.05). The subjective evaluation results...
Introduction

Skin is the largest organ of the human body, and its aging is a complex process caused by a variety of endogenous and exogenous factors [1]. Endogenous aging is inherent, that is, natural aging that develops over time. Exogenous aging mainly refers to photo-aging, which is caused by environmental factors including ultraviolet (UV) exposure. The clinical manifestations of naturally aging skin are decreased skin thickness, dryness and fine wrinkles [2]. However, the clinical manifestations in the skin caused by photoaging are deep wrinkles, roughness, relaxation, spotted pigmentation, telangiectasia and various skin tumors [3].

Exogenous aging damage caused by skin exposure to ultraviolet light (UV) is slow. UV radiation can affect skin pigment metabolism [4]. The immediate response is an increase in the reactive synthesis of melanin and its redistribution, and the delayed response is an increase in the number and vitality of melanocytes [4]. UV can upregulate the expression level of vascular endothelial growth factor (VEGF), resulting in the proliferation and expansion of capillaries [5]. At the same time, UV has an autoimmune inhibitory effect, resulting in the changed number and vitality of immune cells, and the expression of related cytokines [6]. The most relevant feature of photoaging caused by UV is the changes in the proportion, quality and function of the dermal extracellular matrix [7]. The main components of the dermal extracellular matrix are the collagen fiber network, elastic fiber network and proteoglycan [8]. The elastic fiber network provides elasticity to the skin, while proteoglycan plays a role in moisturizing and biological signal transduction. In exogenously damaged skin, these three components have undergone specific changes.

Dextran is a homopolysaccharide composed of glucose as monosaccharide, and glucose units are connected by glycosidic bonds [9]. According to the type of glycosidic bond, dextran can be divided into α-dextran and β-dextran. Dextrose is a kind of widely studied and used α-dextran. In animal models, dextran materials showed good soft tissue filling effect and biocompatibility [10,11]. However, there are no relevant reports on clinical research on the therapeutic effects of dextrose on cosmetic dermatology and facial photoaging. Therefore, the purpose of this study was to explore the clinical efficacy of medical dextrose tincture liquid in the treatment of facial photoaging.

Subjects and Methods

Subjects

All volunteers were informed of the purpose of the study in detail and signed the informed consent documents. A total of 34 volunteers were included in the randomized double-blind study. Inclusion criteria: (1) those whose face had symptoms of photo-aging, including dryness, dullness, lack of elasticity, etc.; (2) non-smokers; (3) individuals aged more than 18 years old. Exclusion criteria: (1) women who were menstruating, pregnant or breastfeeding; (2) those with a history of food or drug allergies and ethical contraindications; (3) those who had taken corticosteroids, antibiotics, tretinoin or other anti-acne medications two weeks before treatment; (4) those who had used hormone drugs and immunosuppressant in the past month; (5) those with obvious damage, redness, scars, active skin diseases, inflammation, or infection on the face; (6) those with symptoms of colds, headaches and fever on the day of the test; (7) those who were allergic to injection materials or certain ingredients in injection preparations; (8) those who had injected unknown fillers into the face that had not gone away before treatment.

Informed consent has been obtained from all the participants. This study was approved by the Ethics Committee of Xi’an EVERCARE Medical Beauty hospital (No. 20200501).

Treatment

Medical hyaluronic acid gel (Huaxi Furuida Biomedical Co., Ltd., Jinan, China) was marked as product A, and medical dextrose tincture liquid (Ningxia Miaolang Biotechnology Co., Ltd., Ningxia, China) was marked as product B. According to the random number table method, the subjects were randomized into control and treatment groups (n = 17). Each volunteer randomly selected product A and product B. The volunteers in the control and treatment groups were treated with medical hyaluronic acid gel and medical dextrose tincture, respectively. They received mesotherapy three times with an interval of 28 days. The steps of mesotherapy were as follows. Volunteers cleaned their faces

Conclusion: Medical dextran tincture has obvious effects of moisturizing, increasing luster, improving skin redness, increasing skin collagen content and enhancing skin elasticity.
with mild soap. After topical anesthesia for 20-30 min, the face was cleaned again. Iodophor solution is used for disinfection and deiodination. The whole face was injected with the mesotherapy instrument, the injection depth was 0.8-12 mm, and the skin punctate hemorrhage was the standard. After treatment, the facial treatment area was covered with a sterile facial pack for 20-30 min.

**Image Analysis**

On the 0th, 28th, 56th and 84th day of treatment, visual images of the face were collected by VISIA image acquisition as previously described [13].

**Skin Detection and Analysis**

On the 0th, 28th, 56th and 84th day of treatment, skin moisture content test, skin gloss test, skin heme content test, skin collagen density test and skin elasticity test were carried out by MPA10 skin tester (CK, Germany) and Derma-lab skin tester (CORTEX, Denmark). The effects of those two products on skin moisture content, skin gloss, skin tone, and anti-aging were assessed through the changes in those indexes. The test environment was 20.0°C-22°C, with a humidity of 40.0%RH-60.0%RH. At the junction of the middle line of the left eye and the nasal wing, the moisture content of the stratum corneum, skin gloss and skin heme were measured. The skin collagen density and skin elasticity were measured at the junction of the middle line of the right eye and the nasal wing.

**Subjective Evaluation**

For subjective evaluation by doctors, two dermatologists scored the degree of facial photoaging before treatment and after a course of treatment according to the VISIA image. The scoring standard was shown in Table 1. For subjective evaluation by volunteers, volunteers rated themselves in terms of skin color, wrinkles, luster, elasticity and moisturizing on the 28th day after each treatment. 0 points for deterioration, 1 point for ineffectiveness, 2 points for slight improvement, 3 points for obvious improvement and 4 points for complete improvement.

**Evaluation Indexes**

On the 0th, 28th, 56th and 84th day of treatment, the visual images of the face were analyzed. The moisture content of the stratum corneum, skin gloss and skin heme, skin collagen density and skin elasticity were analyzed. Skin subjective evaluation of doctors and volunteers was also assessed after treatment.

**Statistical Analysis**

IBM SPSS statistics 22 was used to make descriptive statistics on the measured values and the subjective evaluation scores. The measurement data were expressed as means ± standard deviation (SD). The count data were expressed as a percentage. For the intra-group comparison before and after treatment, the measured values at different time points were compared with the initial values. If the data were normally distributed, t-test was used for statistical analysis. If the data were not normally distributed, t-test was used for statistical analysis.

**Results**

**General Information**

A total of 34 people completed this study. There were 17 volunteers in group A, including 1 man and 16 women, with an average age of 29.59 ± 1.05 years. There were 17 volunteers in group B, including 3 males and 14 females, with an average age of 31.35 ± 1.05 years. There were no significant differences in general information such as gender and age between the two groups (p < 0.05).

**Comparison of Skin Moisture Content Between the Two Groups**

After 28, 56 and 84 days of treatment, the skin moisture contents in group A were significantly increased by 18.0%,

<table>
<thead>
<tr>
<th>Scores</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>The whole face is smooth, without obvious fine wrinkles and uneven pigment in any part of the cheek, forehead and eyes.</td>
</tr>
<tr>
<td>1</td>
<td>There is obvious roughness, uneven pigment (pigmentation or hypopigmentation) or fine wrinkles on one of the above three parts of the whole face.</td>
</tr>
<tr>
<td>2</td>
<td>There are obvious roughness, uneven pigment or fine wrinkles on two of the above three parts of the face, or rough, uneven pigment and fine wrinkles in one part at the same time.</td>
</tr>
<tr>
<td>3</td>
<td>There are obvious roughness, uneven pigment or fine wrinkles on the above three parts of the face, or rough, uneven pigment and fine wrinkles in two parts at the same time.</td>
</tr>
<tr>
<td>4</td>
<td>There is any situation heavier than 3 points on the face.</td>
</tr>
</tbody>
</table>
Comparison of Skin Erythema Index Between the Two Groups

In group A, there was no significant difference in the changes in skin erythema index after 28 days, 56 days and 84 days of treatment in comparison with those before treatment ($p > 0.05$), indicating that product A had no significant change in skin heme contents (erythema index). In group B, the average skin heme content (erythema index) of volunteers before treatment, 28 days, 56 days and 84 days after treatment were 351.8 ± 15.2, 332.9 ± 13.4, 313.4 ± 11.2 and 303.0 ± 18.0, respectively. Compared with that before treatment, the changes in skin erythema after treatment with product B were statistically reduced by 4.8%, 10.0% and 13.1% ($p < 0.001$, Figure 3). Taken together, product B can significantly reduce skin erythema index and improve skin redness.

Comparison of Skin Collagen Density Between the Two Groups

Although skin collagen density after treatment with product A was higher than that before treatment, the effect of...
4.4% and 5.4% respectively. After 28, 56 and 84 days of treatment, the skin retraction time in group B was decreased by 9.5%, 11.2% and 14.8% respectively in comparison with that before treatment ($p < 0.001$, Figure 5). As described above, product B can significantly reduce skin retraction time and enhance skin elasticity. The effect of product B on skin elasticity was significantly earlier than that of product A, and the effect of improving skin relaxation was better than that of product A.

Comparison of Subjective Assessments of Doctors and Volunteers Between the Two Groups

Skin retraction time is one of the indicators to measure skin elasticity. It refers to the time required for the skin to fully lift and retract to 33% of the peak height. The shorter the retraction time, the better the elasticity of the skin. After 56 and 84 days of treatment, compared with before treatment, the skin retraction time of product A group decreased by 4.4% and 5.4% respectively. After 28, 56 and 84 days of treatment, the skin retraction time in group B was decreased by 9.5%, 11.2% and 14.8% respectively in comparison with that before treatment ($p < 0.001$, Figure 5). As described above, product B can significantly reduce skin retraction time and enhance skin elasticity. The effect of product B on skin elasticity was significantly earlier than that of product A, and the effect of improving skin relaxation was better than that of product A.

Comparison of Skin Elasticity Between the Two Groups

Skin retraction time is one of the indicators to measure skin elasticity. It refers to the time required for the skin to fully lift and retract to 33% of the peak height. The shorter the retraction time, the better the elasticity of the skin. After 56 and 84 days of treatment, compared with before treatment, the skin retraction time of product A group decreased by

![Figure 3. Changes in skin heme content before and after treatment.](image1)

![Figure 4. Changes in skin collagen density before and after treatment.](image2)
The skin color became brighter, the pores narrowed and the gloss increased. Figure 8B showed a case of skin redness and uneven complexion improvement (volunteer No. 25, VISIA standard light source mode). After three instances of treatment with product B, the volunteer’s skin turned red, and the uneven skin color was significantly improved. The skin color was uniform, and the skin became bright and white. Figure 8C showed a case of skin redness improvement (volunteer No. 38, VISIARed Areas light source mode photo). After three instances of treatment with product B, the volunteer’s skin redness was significantly improved, the color of erythema became lighter, the red area became smaller, and skin inflammation was decreased. Figure 8D showed a case of skin redness and roughness improvement (volunteer No. 8, VISIA standard light source mode). After three instances of treatment with product B, the volunteer’s skin dullness and roughness were significantly improved, the skin color became brighter, the pores narrowed and the gloss increased.

Discussion

Water light therapy is the accurate injection of nutrients or drugs into specific layers of the skin through hollow microneedles, which can effectively supplement nutrients, such as hyaluronic acid and vitamins [13]. Moreover, it can stimulate collagen production, make the skin moist and shiny, effectively delay skin aging and improve skin quality [14]. It can also treat diseases by injecting drugs [15]. The common drugs and components used in water light therapy can be divided into simple use of hyaluronic acid, non-crosslinked hyaluronic acid as carrier, matching with different nutrients, collagen preparation, mixed growth factor series, cocktail formula with multiple components or focusing on one component, polydeoxynucleoside, etc. [16].
Dextran is a kind of branched dextran polymer with molecular weight ranging from 1 kDa to 2000 kDa. The side chain degree of dextrose differs according to molecular weight [17]. The smaller the molecular weight, the lower the side chain degree. The closer the molecular weight distribution is, the different application emphases of different molecular weights are different [18]. Compared with other polymer materials, dextran has the advantages of good water solubility, biodegradability, small antigenicity and high safety, and it has been used as a plasma substitute in clinics [19, 20]. Therefore, dextran with the above characteristics has important application value in the field of skin rejuvenation treatment. The cross-linked dextran filler (Lipen De, Cheonghwa Medipower Corporation, Jangseoung, Korea) was approved by the Korean food and Drug Administration in 2012. Shin and his team have confirmed that it has a filling effect for more than six months for the treatment of nasolabial folds [21].

In this study, we explored the therapeutic effect of medical dextran as a new type of water-light injection material on skin photoaging. Our results showed that compared with that before treatment, medical dextran significantly increased skin moisture retention and skin gloss after 84 days of treatment. It showed that medical dextran can significantly improve the roughness of the skin and increase the moisture content of the skin stratum corneum. In terms of moisturizing and improving skin gloss, medical dextran has the same improvement effect as sodium hyaluronate. Compared with that before treatment, medical dextran treatment significantly reduced skin erythema and redness. However, sodium hyaluronate had no significant effect in improving skin erythema. Compared with that before treatment, medical dextrose treatment significantly increased skin collagen density, stimulated collagen production, and has an anti-aging effect. Particularly, the significant difference in the effect of medical dextran on skin collagen density appeared earlier than that of sodium hyaluronate, indicating that medical dextran can start and promote collagen regeneration faster. Compared with that before treatment, medical dextrose treatment can significantly reduce the skin retraction time, indicating that it can improve skin sagging problems, and the effect was significantly better than with sodium hyaluronate.

The subjective evaluation results of doctors showed that after 84 days of treatment with medical dextran and sodium...
hyaluronate, the overall score of the volunteers’ photoaging was significantly reduced in comparison with that before treatment, indicating that they can significantly improve skin photo-aging problems, including skin roughness, dryness, lack of elasticity, etc. From the subjective evaluation results of volunteers, as the time of treatment increased, the percentage of positive responses from volunteers in various aspects, such as dry skin, skin gloss, uneven skin tone and dullness, skin elasticity, and skin wrinkles, gradually increased. Especially for gloss and elasticity, the overall improvement with medical dextran is better than with sodium hyaluronate.

Conclusion

In conclusion, medical dextran has obvious effects of increasing moisture content, increasing luster, improving skin redness, increasing skin collagen and enhancing skin elasticity. Medical dextrose is superior to hyaluronic acid in improving skin redness and skin relaxation.

References

Stardust Pattern as Evolution of Pigmented Spitz Nevi During Childhood

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Key words: spitz nevus, starburst, stardust


Accepted: July 4, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Spitz nevi (SN) are benign melanocytic proliferations frequently occurring in children. Some pigmented SN with a starburst pattern evolve into the “stardust” one, which is characterized by a central, black to gray, hyperpigmented area and remnants of a brown network at the periphery. These dermoscopy changes are often the first alert to induce excision.

Objectives: The aim of this study is to enlarge the case series of stardust SN in children, in order to increase confidence with this new dermoscopic pattern and reduce unnecessary excisions.

Methods: This retrospective observational study was conducted with SN cases received from IDS members. The inclusion criteria were: clinical and/or histopathologic diagnosis of Spitz naevus with starburst appearance in children <12 years old, availability of a dermoscopic image at baseline and after follow-up of at least 1 year, availability of patient data. The dermoscopic images and their changes over time were assessed by three evaluators in consensus.
**Introduction**

Spitz nevi (SN) are benign melanocytic proliferations that frequently occur in children [1]. 50% to 75% of patients with a diagnosis of Spitz nevi are found to be younger than 20 years of age and the overall incidence has been estimated between 1.4 and 7 new cases per 100,000 persons per year [2].

Before 1948, this entity was defined as Juvenile melanoma, as the clinical and histological differentiation between Spitz Nevus and melanoma of the adult could not be made with certainty in several cases.

Sophie Spitz [3] first noted a difference in the biological behavior of Spitz nevus compared to adult melanoma. In a series of 13 lesions diagnosed as malignant melanoma in children, only one patient died from melanoma metastases. The other 12 participants had lesions that were locally excised without recurrence or metastases. Sophie Spitz concluded that, since metastases from juvenile melanomas occur only rarely, conservative surgery, rather than the radical surgery usually indicated for adult melanomas, seems justified. The study challenged the standard of practice at that time relating to the diagnosis of melanomas and benign nevi in children [4].

However, in the late 1990s, a new era of controversies on the management of spitzoid lesions started, because cases of spitzoid lesions without malignant histopathological criteria but with nodal metastasis were described. New histological entities were introduced attempting to classify spitzoid tumours with intermediate histopathological features between Spitz naevus and spitzoid melanoma (Spitz naevus with atypia and metastasis, metastasizing Spitz tumour, atypical Spitz naevus, melanocytic tumour of unknown malignant potential, melanocytoma). The worrying scenario of possible loco-regional dissemination in connection with the medico-legal liability could lead to the risk of overcalling [5].

The introduction of dermoscopy significantly improved the diagnosis of Spitz naevi, as they were shown to exhibit a peculiar and characteristic pattern of dermoscopic structures.

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**Results:** 38 SN were enrolled, with a median age of 7 years and a median FUP duration of 15.5 months. Comparing the evolution with time of FUP, no significant differences were found between growing and involuting lesions in terms of patient age and sex, location and palpability of lesions.

**Conclusions:** The long follow-up reported in our study could really support the concept of benignity of changing SN. A conservative approach is acceptable for nevi showing the starburst pattern, because it may be considered a physiological evolution of pigmented Spitz nevus, and urgent surgeries could be avoided.

Pigmented variants were first investigated and shown to display the so-called ‘starburst’ pattern, consisting of a central area of homogeneous black-blue pigmentation and symmetrically distributed peripheral streaks or pseudopods [6].

Several additional patterns were later found to be associated with pigmented Spitz naevus, including globular, homogeneous, reticular and multicomponent patterns.

Histologically, Spitz nevi are composed of spindled and/or epitheloid melanocytes with large nuclei and abundant cytoplasm [7]. The melanocytes seen in Spitz nevi are often larger than those in other types of nevi, arranged perpendicular and parallel to the skin surface, highly cohesive, and they do not destroy the nearby keratinocytes. These spindle cells contain melanin pigment. Additionally, Kamino bodies, which are rounded eosinophilic globules, are often seen. Frequently, solitary melanocytes and nests of melanocytes occurring above the dermo-epidermal junction are detected. Dermal nests and cords of cells could be seen if a dermal component is present. The lack of ulceration, dermal sheets of cells, or significant mitotic activity could exclude the diagnosis of malignant tumors [8]. Guidelines for the management of spitzoid-looking tumors have been proposed by the International Dermoscopy Society (IDS) in 2017 [6].

The first management criterium is symmetry. Lesions displaying asymmetrically distributed spitzoid features (peripheral streaks/pseudopods, dotted vessels, reticular depigmentation) should be excised to rule out melanoma. In symmetrical lesions, the second management-driven criterium is age. Dermoscopically symmetric spitzoid-looking lesions developing after the age of 12 years should be managed with caution because there is a considerable probability that these lesions actually constitute melanoma. Below the age of 12 years, the recommended management of dermoscopically symmetric spitzoid-looking lesions depends if the lesion is nodular or flat, which is the third criterium. For nodular lesions, the recommended management is excision, mainly because the possibility of an atypical Spitz tumor cannot be excluded on the basis of dermoscopic morphology. For flat/raised lesions, follow-up until stabilization is suggested. Monitoring is highly recommended in the subset of lesions displaying a starburst pattern (Reed naevi). Lesions displaying a starburst...
pattern are expected to grow (Fig 1.), reach stabilization and, then, involute. Ideally, the typical Reed naevus grows symmetrically and gradually acquires a blue-black homogeneous aspect with the disappearance of peripheral projections. After years, the dark pigmented area is gradually restricted to the center of the lesion, while the peripheral part of the naevus exhibits remnants of a delicate brown network. (Fig 2-3-4). This pattern, which may anticipate the involution of the lesion, was first described by Argenziano et al. [1] and later named “stardust” pattern.

Figure 1. A-B) Male patient aged 5, at his first visit for a SN on the knee. Dermoscopy shows typical SN with hyperpigmented central area and pseudopods at the periphery. C-D) After 1 year, the lesion starts losing pseudopods and grows symmetrically.

Figure 2. First and last image of SN in a female patient aged 11 and 20 respectively. The classic stardust pattern is evident in the second dermoscopy.
Primary lesion, sex, date of birth, age at first and at last visit, number of follow-up visits and number of total months of follow-up. The dermoscopic images were assessed by three evaluators in consensus (GB, CS and GA), with the stardust feature scored as present when at least two of them were in agreement. Cases not assessed as “starburst pattern” were excluded. Moreover, change in dimension (if present stated as growth or involution), palpability at first visit, and eventually change over time were also scored as present when at least two evaluators were in agreement.

Results

We reviewed clinical and dermoscopic images of 38 SN in patients aged from 1 to 12 years (median age, 7 years p<0.01). 21 males and 17 females were included. All patients were Caucasian. The follow-up period varied from a minimum of 3 to a maximum of 120 months, with the median FUP duration of 15.5 months. The median number of follow-up visits was 2.0 with a minimum of 1 and a maximum of 10 (IQR 3.75).

Of 32 SN, 27 (71.1%) were located on the extremities, 3 (7.9%) on the head and 8 (21%) on the trunk.
With regards to the clinical presentation at baseline, 36 SN were flat/raised (94.7% - 95% CI: 80.9% to 99.1%, p<0.01) and only 2 were nodular (5.3% - 95% CI: 0.9% to 19%, p<0.01). Almost all the lesions remained flat at the last follow-up visit (97.4% - 95% CI: 84.6% to 99.9%, p<0.01) while 1 of the 2 nodular lesions became flat after regression (2.6% - 95% CI: 0.1). Between the first and the last visit 63.2% of the lesions (N:24 – 95% CI: 46% to 77.6%, p<0.01) had an increase in size, 26.3% had a reduction in size (N:10 – 95% CI: 14% to 43.4, p=0.05) while 10.5% (N:4 – 95% CI: 3.4% to 25.7%, p=0.14) had only dermoscopic changes without variation in dimension.

Comparing the evolution with time of follow-up, no significant differences were found between growing and involuting lesions in terms of patient age and sex, location and palpability of lesions.

Dermoscopic examination showed findings consistent with the literature.

The starburst pattern evolved into stardust over time. First, a growing phase is observed in which the center of the lesion remains black/blue and the periphery presents a brown network. Successively, an involution phase starts with regression of the network in the periphery and ends with a grey granular pattern in the center of the lesion.

**Conclusions**

Our study revealed that the Stardust pattern is more frequent in the extremities, with no differences between sex. The median age is consistent with the literature.

Barnhill et al. [11] already described an association between pigmented SN and thighs, whereas the rapidly growing, pink-to-reddish papule variant is more frequent in the head and neck region.

Analyzing the follow-up, we noted that the time needed to pass into a growth phase and then into an involuting one is very variable. The onset of the growth phase ranged between 4 to 24 months from first appearance. Surprisingly, we observed a SN that turned into stardust pattern after being stable for 10 years (Fig 4), while another SN after 10 years was almost completely involved showing greyish remnants of the network (Fig 5). It should be remembered

![Figure 4](image_url)

**Figure 4.** A-B) SN in a patient aged 6 at first visit. At dermoscopy, the lesion shows blue-white center with brown streaks at periphery. C-D) Same lesion at 17 years old. Dermoscopy highlights stardust pattern with blue globules in the center on a brown background and brown network fading out at the periphery.
that the IDS guidelines suggest continuing follow-up also for nevi undergoing involution until stabilization (documented evidence of no change for at least 6 months) or complete disappearance. The reason for this SN dynamic behavior is not clear, but can be related to the genetics of melanocytic cells. The most frequently observed genetic alterations in Spitz nevi involve the HRAS gene that drives the symmetrical overgrowth of cells with epithelioid morphology via preferential PI3K/AKT activation [12]. The acquisition and loss of mutations are responsible for the growth and involution of Spitz nevi.

In our series, despite the change in dimension or in dermoscopy pattern, the symmetry was always maintained as well as the flat/raised appearance as none became nodular.

The long follow-up reported in our study could really support the concept of benignity of changing SN. Since Spitz nevi are not precursors of melanoma [6], clinically and dermoscopically typical cases of SN will maintain the same biological behavior, regardless of dermoscopic changes. Moreover, a flat/raised dermoscopically symmetric spitzoid-looking lesion below the age of 12 has an extremely low possibility to be a melanoma as pediatric melanoma is very rare and melanomas arising in children are often nodular and/or amelanotic [13].

A limitation of our study is that our sample is small and descriptive estimates are weighted by large confidence intervals. Other studies are needed to explore the different patterns of evolving SN, and to combine dermoscopy, confocal microscopy and genetic mutations in the optics of the new concept of deep phenotyping.

In conclusion, although the decision to cut off a lesion is demanded to an overall consideration of clinical context (age, site) and guidelines management, a conservative approach is acceptable for nevi showing the stardust pattern, because it resulted to be a physiological evolution of pigmented Spitz nevus, and urgent surgeries could be avoided for these patients.
References

Digital Ulcers: Multidisciplinary Approach and Dermatological Management

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Key words: digital ulcer, multidisciplinary approach, dermatology, diabetes, ischaemic wound


Accepted: June 9, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introducción: Digital ulcers represent a current public health issue, due to the relevant difficulties in their management and their tendency to become chronic, non-healing lesions.

Objectives: Our case series represents an opportunity to discuss the main comorbidities of digital ulcers and to present an evidence-based treatment protocol that has proved highly effective in our clinical practice.

Methods: We collected the clinical data about clinical features, associated diseases and diagnostic and therapeutic procedures of 28 patients with digital ulcers referred to our Wound Care Service at S. Orsola-Malpighi Hospital.

Results: Digital ulcers were divided into 5 categories, based on the causative agent: peripheral artery disease: 5/16 females and 4/12 males, diabetes-associated wounds: 2/16 females and 1/12 males, mixed wounds: 4/12 males, pressure wounds: 3/16 females and 2/12 males, and immune-mediated diseases associated with wounds: 6/16 females and 1/12 males. Each group received specific management, based on the characteristics of the ulcer and the underlying comorbidities.

Conclusions: The clinical evaluation of digital wounds requires a thorough knowledge of their aetiology. A multidisciplinary approach is necessary to achieve a precise diagnosis and correct treatment.
Introduction

With the increase in life expectancy, more and more patients are suffering from chronic diseases and an increasingly innovative and personal approach, which includes the collaboration between specialists from various branches of medicine and surgery, is now part of a comprehensive care plan [1].

Limb chronic ulcers have an increasing incidence, due to the higher prevalence of chronic vascular and metabolic diseases, such as peripheral artery disease (PAD) and diabetes mellitus, which play the main role in their aetiology.

Within the category of limb chronic ulcers, digital ulcers (DU) represent a small but peculiar group, due to their difficult management and their scarce tendency to heal.

We present an observational study of 28 patients with DU referred to our Wound Care Service, focusing on multidisciplinary and dermatological management.

Methods

We collected the clinical data of patients with DU referred to the Wound Care Service (a tertiary referral center) of the Dermatology Unit of the S.Orsola-Malpighi Hospital over a period of 18 months, from January 2020 to June 2021. Only patients presenting with non-healing digital ulcers of the limbs, present for at least 6 weeks, were enrolled. Demographic and clinical data were collected, including associated comorbidities and their therapy and previous ulcerative episodes in other cutaneous areas. Diagnosis of the disease that caused the DU was based on clinical history, laboratory evaluation and histopathological study, when necessary. Management of these conditions was based on the main International Guidelines for the management of peripheral artery disease in patients with foot ulcers and diabetes [2-4] and on the evidence-based protocol for diabetic foot ulcers [5].

All the digital wounds were assessed for excluding any signs of local or surrounding infection. In particular, the presence of at least 3 or more STONEES criteria (Size is bigger, Temperature elevated, Os, New breakdown, Exudate, Erythema, Smell) lead to a systemic antibiotic treatment. The presence of at least three NERDS criteria (Nonhealing, Exudate, Erythema, Smell) lead to a systemic antibiotic treatment. The presence of at least three NERDS criteria (Nonhealing, Exudate, Erythema, Smell) lead to a systemic antibiotic treatment. The presence of at least three NERDS criteria (Nonhealing, Exudate, Erythema, Smell) lead to a systemic antibiotic treatment.

The evaluation of pain associated with the DU was performed using the VAS (visual analogue scale). All patients with pain equal or superior to 5 on the VAS scale, despite adequate medication and non-responder to paracetamol, were managed by our Pain Therapy Service.

Despite the cause of the DU, mechanical debridement of the necrotic tissues was performed in all cases. In three cases, the use of local medications was preceded by a total surgical debridement of necrotic tissue. In the other patients, an ambulatorial mechanical debridement was performed. Gauze soaked in iodine was used as the main antiseptic medication.

Results

From January 2020 to June 2021, we treated 28 patients with DU, 12 males and 16 females (Table 1). Median age was 72.6 years (range 38-97 years): average age of males was 68.3 years, that of females 75.9 years. The toes were the most common site of DU (24 patients), with 16 patients having ulcers of several digits (ranging from 2 digits to 4); finger ulcers were present in 4 patients, one of them having DU in 3 fingers, the other 3 in one finger.

The diseases detected as causes of DU were as follows: peripheral artery disease (PAD): 9 cases, all with DU of the toes; type 2 diabetes mellitus with poor glycaemic control: 3 patients, all with DU of the toes; association of PAD with type 2 diabetes mellitus: 4 patients, 3 with DU of the toes and 1 of a finger; pressure ulcers with toe involvement: 5 patients; vasculitis: 3 patients with DU of the toes; systemic sclerosis (SSc) in 4 patients, 3 with DU of the fingers and 1 of a toe.

PAD-Associated DU

The 9 patients with PAD were evaluated by specific imaging investigation (color duplex ultrasound, computed tomographic angiography, magnetic resonance angiography) and then referred to a vascular surgeon for possible revascularization. Only 4 cases were revascularized, while in the other 5 the procedure was not possible due to the poor general conditions and the high anaesthetic risk. The topical medication of the DU after debridement in all these patients was an Iodine-based antiseptic dressing or a soft silicon foam dressing, in order to diminish the risk of bacterial superinfection of necrotic tissue (Figure 1a). All the cases that underwent revascularization showed a better outcome compared to the other cases, with a significant reduction in healing times. No correlations with any lymphatic drainage impairment were found in this group of patients after specific imaging investigation.

Diabetes-Associated DU

Seven patients presented type 2 diabetes mellitus in poor glycaemic control, associated with the presence of DU. In 3 cases diabetes was identified as the primary cause of the ulcerative lesions, as laboratory and technical evaluations excluded other comorbidities: these patients were referred to the Diabetology service for a review of their metabolic status and chronic hypoglycaemic therapy and underwent local medications with gauze soaked in iodine to accelerate wound healing. A better clinical outcome was achieved only after the diminishment of these patients’ plasma glucose values.
In 4 patients, type 2 diabetes was associated with arteriopathy of the large vessels of the lower limbs that required prompt revascularization (Figure 1b). Surgery increased the chances of wound healing in these patients.

Obesity and metabolic syndrome are often present in patients with diabetes II and PAD, as they recognize a sedentary lifestyle as a common denominator, associated with unbalanced nutrition. However, no direct correlations were found between these factors and the development of digital ulcerative lesions.

**Pressure DU**
Five patients with pressure ulcers of the feet developed toe lesions as an effect of continuous forces directed to the distal pulp, causing progressive skin ischemia above bone prominences. These patients were bedbound due to progressive neurological diseases, such as multiple sclerosis with spinal involvement (4 cases) or a severe form of motor-sensitive polyneuropathy of the lower limbs (1 case). In these cases, mechanical debridement of the eschar followed by topical therapy with iodine gauzes was associated with a physiatrist consultation that lead to the prescription of plantar orthosis and anti-decubitus mattresses. All the procedures allowed wound healing with restoration of the physical integrity of the toe skin (Figure 1c).

**Immune-Mediated Disease-Associated DU**
Four patients, 3 with DU of the fingers and 1 of a toe suffered from SSc (Figure 1d). A skin biopsy of the DU showed in all cases skin calcinosis. These patients were managed through the close collaboration of rheumatologists.

One patient with DU of the toe was affected by rheumatoid arthritis and 2 by systemic lupus erythematosus. A biopsy of the perilesional skin showed leukocytoclastic vasculitis with fibrinoid necrosis of the vessel walls and prominent polymorphonuclear cell infiltration.

<table>
<thead>
<tr>
<th>Patient</th>
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<td>70</td>
<td>M</td>
<td>2</td>
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<td>toe</td>
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<td>3</td>
<td>finger</td>
<td>SSc</td>
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</tr>
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<td>F</td>
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<td>toe</td>
<td>PAD</td>
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<td>19</td>
<td>84</td>
<td>F</td>
<td>2</td>
<td>toe</td>
<td>Pressure ulcer</td>
</tr>
<tr>
<td>20</td>
<td>56</td>
<td>F</td>
<td>1</td>
<td>toe</td>
<td>SSc</td>
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<tr>
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<td>80</td>
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<td>2</td>
<td>toe</td>
<td>PAD</td>
</tr>
</tbody>
</table>

M: Male; F: Female; PAD: peripheral artery disease; SSc: systemic sclerosis.

Table 1. Clinical characteristics of the patients with digital ulcers.
and on the respective aetiologies. The multidisciplinary management of the different cases represents the standard model to get better the outcome of patients suffering from multiple comorbidities.

**Discussion**

Our literature search could not identify any studies that collected such a large number of cases regarding DU of both fingers and toes, making a subdivision based on clinical aspects and on the respective aetiologies. The multidisciplinary management of the different cases represents the standard model to get better the outcome of patients suffering from multiple comorbidities.

**PAD-Associated DU**

The term peripheral arterial disease defines the lower extremity artery disease, including obstruction at the aortoiliac, femoropopliteal and infrapopliteal arterial segments [5]. Studies have shown an increased risk of cardiovascular mortality, as well as of morbidity from myocardial infarction.
and stroke in patients with asymptomatic or symptomatic arterial disease [2]. The distal localization of the vascular obstruction leads to the formation of chronic ulcerative lesions of the acral extremities, mainly of the lower limbs, with the appearance of necrotic eschars of the distal phalanges of the toes. These ulcers are at high risk of bacterial superinfection. The association with both uncontrolled type II diabetes mellitus is common, therefore in these patients, the evaluation of the arterial function with imaging techniques should always be associated with laboratory monitoring of the glycaemic state, as type II diabetes comorbidity greatly impairs local wound management [6].

The symptoms and signs of PAD are variable and range from the classic symptom of claudication to other non-joint-related limb symptoms (atypical leg symptoms) or are absent [7-10]. In these cases, the DU may be the first sign that leads to the diagnosis. The vascular examination for PAD includes pulse palpation, auscultation for femoral bruits, and inspection of the legs and feet [8]. To confirm the diagnosis of PAD, abnormal physical examination findings must be confirmed with diagnostic testing [5]. Studies for anatomic imaging assessment (duplex ultrasound, computed tomography angiography [CTA], or magnetic resonance angiography [MRA], invasive angiography) are generally reserved for highly symptomatic patients in whom revascularization is being considered [9].

Patients with PAD associated with skin ulcers fall into a high-risk cardiovascular group, due to the signs of advanced disease: for this category, a careful multidisciplinary evaluation is important in order to select patients eligible for surgical revascularization and to increase the chance of wound healing, as well as of reducing a progression of disease [11].

Adequate pharmacological therapy associated with a healthy lifestyle is mandatory for the chronic management of this disease and to reduce the global cardiovascular risk [12, 13].

Diabetes-Associated DU

As for diabetic foot ulcers, they occur in between 12 and 25% of patients with type 2 diabetes mellitus [14] and precede 84% of all non-trauma limb amputations in this growing slice of the population [15].

A diabetic foot ulcer is defined as any skin breakdown on the foot of a diabetic person [16]. Early recognition of the skin defect and treatment prevents its progression to a chronic wound that is often recalcitrant to therapy [17-18].

When a patient with a diabetic foot ulcer is first seen, a comprehensive history and treatment plan must be put into place. Then, a laboratory evaluation based on their metabolic status, and the monitoring for any complications (e.g. heart disease, renal failure, retinopathy, neuropathy) must be carried out [19]. It is important to assess the pedal pulses, and unless a pulse is clearly palpable, all patients with foot ulcers should undergo non-invasive vascular testing, to determine if the patient would benefit from revascularization. In an observational study, shorter time to revascularization (<8 weeks) was associated with a higher possibility of healing of ischaemic foot ulcers [20]. In addition, it is mandatory that every patient be evaluated for proper orthotics, and appropriate footwear should be prescribed that adequately protects the foot from trauma induced by shoes and alleviates pressure, considering the fact that pressure and pain sensation are often impaired in these patients [21].

Pressure DU

Prolonged bed rest caused by paraplegia and various central nervous system diseases plays an important role in the formation of pressure acral lesions, which follow prolonged skin ischemia and are especially located above bony prominences. The first signs of ischemia are the formation of calluses at the level of the toepads. If not recognized and treated, they lead to the formation of painless and difficult-to-treat chronic ulcers. The application of physical means such as intermittent pneumatic compression devices and the evaluation from expert physiotherapists is necessary in these patients, in order to prevent the extension of the wound and the arising of other similar lesions in other toes [22].

In people suffering from advanced neurological conditions, spasticity is significantly associated with the development of pressure ulcers in typical and even atypical locations [23]. Severe spastic conditions might facilitate wound onset in various ways: increased tonus of the limbs leads to immobility and to a reduced capacity to reposition the body, with an abnormal pressure redistribution. This prolonged rigidity causes severe soft tissue injury [4, 24]. A comprehensive assessment is warranted with a focus on identifying the source of pressure, contributing factors, underlying comorbidities, and elements affecting wound healing.

Pressure redistribution targeting the duration and/or magnitude of loading is critical [25, 26]. Evidence exists that advanced support surfaces are superior to standard hospital beds in preventing and managing pressure injuries. However, no clear advantage has been identified for one specific advanced support surface over another [27].

There is strong evidence that a moist wound environment accelerates healing in this type of DU: occlusive dressings seem to be superior to more-traditional simple gauze, especially in terms of maintaining a moist wound environment [28]. Ultimately the dressing selection may be guided by the characteristics of the wound, balance of moisture and exudate, bacterial control, debridement balance, ease of use, cost, and patient preference [29].
**Immune-Mediated Disease-Associated DU**

Inflammatory and autoimmune systemic diseases may first become clinically evident with the appearance of an ischemic digital wound. SSc is the best described among these types of conditions [30]. Cutaneous and/or systemic vasculitis can also present with the formation of necrotic lesions involving the fingers of the limbs, both the upper and lower ones. SSc is an immune-mediated disease that represents a major clinical challenge for physicians and patients. For the patient, SSc is associated with great uncertainty of outcome and development of manifestations that are potentially lethal or can reduce quality of life [31].

The problem of digital ulcers is increasingly recognised [32]. DU occur in around half of SSc cases during their disease history, and about one in five patients might have this complication at any one time [33, 34]. There is now a better appreciation of the effects of digital ulcers, which include impaired function, pain, and loss of employment, as well as the more obvious medical complications of cellulitis, osteomyelitis, digital infarction, and severe pain. Treatment of digital ulcers with drugs or systemic therapies needs to be combined with appropriate expert local care and dressings, and this treatment usually benefits from specialist nurse input. Evidence-based treatments include phosphodiesterase-5 inhibitors and endothelin receptor antagonists, although some studies have not shown a clear treatment benefit [35, 36].

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disorder expressed most commonly as a symmetrical, deforming arthropathy [37]. A well-known cause of ulceration in rheumatoid arthritis is vasculitis. Vessels of different sizes may be affected. These patients will require systemic therapy because mortality can be high [38].

Workup for the patients should include a complete history and thorough physical exam, screening laboratory studies and biopsies. Treatment is a challenge, but stabilizing the autoimmune disease is imperative. Adalimumab with methotrexate (MTX) has shown promise in RA-associated ulcers [39]. Improving wound bed preparation by the application of moisture-retentive dressings has been shown to be beneficial [40].

Systemic lupus erythematosus (SLE) is a systemic autoimmune connective tissue disease that can affect most organ systems. Ulcers are not infrequent and, like other connective tissue diseases, they are multifactorial [41]. Vasculitis, noninflammatory thrombosis of small or large vessels, venous insufficiency, lupus profundus, lichen planus overlap, and drug-induced lupus syndrome has been associated with leg ulcerations. The ulcers are usually painful, sharply marginated, or punched out. Adjacent skin can appear erythematous, purpuric, or rolled and violaceous. Histological examination of vasculitis ulcers in SLE shows a leukocytoclastic vasculitis with fibrinoid necrosis of the vessel walls and prominent polymorphonuclear cell infiltration. Thrombocclusive histologic findings can be associated with the presence of antiphospholipid antibodies (lupus anticoagulant) [42]. SLE-associated leg ulcers are a therapeutic challenge, as local wound care is not always sufficient. The underlying cause of the ulceration needs to be established and treated. If vasculitis is present, systemic corticosteroids with cytotoxic agents should be utilized [37].

**Conclusion**

The clinical evaluation of DUs requires a thorough knowledge of their possible causes. A careful clinical evaluation is necessary together with laboratory and imaging technique investigations. A multidisciplinary approach in the management of these wounds is the only effective way to achieve a precise diagnosis and a correct treatment, as described in Figure 2.

---

**Figure 2.** Clinical evaluation in the management of digital wounds. NERDS: Nonhealing, Exudate Increase, Red friable granulation, Debris; STONEES: Size is bigger, Temperature elevated, Os, New breakdown, Exudate, Erythema, Smell; VAS: visual analogue scale; ECD: echo colour doppler; AD: autoimmune disease.
References


11. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ. Published online February 1, 2018:j35842. doi:10.1136/bmj.j35842


Introduction: Chronic urticaria is a common disease, characterized by the development of wheals, angioedema, or both, which can be associated with several comorbidities. Most of the available studies have focused on specific common comorbidities and their association with CU, but have seldom reported the overall burden of comorbidities.

Objectives: This study aimed to investigate and analyze self-reported comorbidities in Polish patients with CU.

Methods: An anonymous online survey consisting of 20 questions was conducted on members of an Urticaria group on the social media platform Facebook. A total of 102 people took part in this survey. The results were analyzed in Microsoft Excel 2016.

Results: In the group, 95.1% were females and 4.9% males, with a mean age of 33.8 years. The most common diagnosed type of urticaria was spontaneous (52.9%). Angioedema accompanied urticaria in 68.6% of the respondents, mainly those with delayed pressure urticaria (86.4%). 85.3% of respondents reported comorbidities, most often atopic diseases and allergies (49%), chronic inflammation and infections (36.3%), thyroid (36.3%) and psychiatric disorders (25.5%). Moreover, in 30.4% of patients, at least one autoimmune disease was noted. As compared to the patients without autoimmune urticaria, many more with autoimmune urticaria had a coexisting autoimmune disease (50% vs. 23.7%). Family history of autoimmune diseases was positive in 42.2%, and the familial history of urticaria and atopy was positive in 7.8% and 25.5%, respectively.

Conclusions: The knowledge of comorbidities of chronic urticaria may support clinicians to manage and treat patients with this common condition.
Introduction

Chronic urticaria (CU), affecting 0.5%–1% of the general population, is defined by the repeated occurrence of itchy hives, angioedema, or both, for 6 weeks or more. According to current guidelines, CU can be divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) with several subgroups. Both CU types can occur concomitantly in the same patient [1]. CU develops more frequently in adults, in the third to fifth decade of life, and females are affected at least twice as often as males [2].

Several studies reported that patients with CU frequently exhibit comorbidities. The association of CU with psychiatric disorders, including depression, anxiety and behavioral problems, atopic disorders, autoimmune disorders, hypertension, osteoporosis, and infections, has been reported previously [3-7]. Most of these studies have focused on specific common comorbidities and their association with CU, but have seldom reported the overall burden of comorbidities.

Objectives

This study aimed to investigate and analyze self-reported comorbidities in Polish patients with CU.

Material and Methods

The study was based on an anonymously filled online survey prepared by the authors. Individuals with CU and parents of children with CU were recruited for participation in the study through closed membership CU support groups found on social media platforms (Facebook). Individuals interested in participating in the survey were directed through an introduction and implicit consent into Google Forms.

The questionnaire consisted of 20 questions: 7 single-choice and 13 multiple-choice. Single-choice questions concerned basic demographic information, presence of angioedema, age of the first episode of CU, and frequency of CU symptoms. Multiple-choice questions concerned information about diagnosed types of CU, localization of angioedema, family history of urticaria and atopy, family history of autoimmune diseases, the coexistence of connective tissue, thyroid gland, digestive system, inflammatory diseases, metabolic and cardiovascular diseases, skin diseases, allergic diseases, mental disorders, neoplasm diseases, and others that individuals could add in a designated place.

Data about family history of atopy was defined as the presence of asthma, eczema, allergic rhinitis, or rhinoconjunctivitis, whereas autoimmune diseases were defined as Hashimoto’s thyroiditis, systemic lupus erythematosus, pernicious anemia, vitiligo, Graves’ disease, rheumatoid arthritis, celiac disease, alopecia areata, sclerosis multiplex, scleroderma, diabetes mellitus type 1, Crohn’ disease and ulcerative colitis.

A total of 102 people (97 women and 5 men) took part in this survey. The average age of patients was 33.8 years (range, 9-57 years). The results were analyzed in Microsoft Excel 2016 and presented on a percentage scale.

The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/833/2021).

Results

The majority of CU patients were 19–39 years old (59.8%), followed by patients aged ≥40 years old (33.3%), while a small proportion, 6.9% of patients were ≤18 years old. The vast majority of the respondents (80.4%) lived in cities, the remaining 19.6% lived in villages. More than half of the respondents (63.7%) reported higher education, 17.6% secondary, and 3.9% vocational. Nearly 16% of respondents were studying.

The mean age at disease onset was 27.5 years (range, 3–55 years). Among all patients, the most frequent type of CU was CSU, diagnosed in 78.4%. Autoimmune urticaria, which is a subtype of CSU, was diagnosed in 25.5%. Among all patients with CU, 59.8% were diagnosed with CSU only, 21.6% were diagnosed with isolated CIndU only and the remaining 18.6% had a combination of both types. The most common subtypes of CIndU were delayed pressure urticaria (21.6%), symptomatic dermographism (14.7%), and cholinergic urticaria (8.8%; fig 1).

Angioedema symptoms were reported by 70 patients (68.6%) and occurred mainly in patients with delayed pressure urticaria (86.4%; fig 2). Of the 70 patients who experienced symptoms of angioedema, the most frequently reported locations for angioedema were non-facial body areas (82.9%), most commonly the hands (68.6%), feet (57.1%), over joints (35.7%), and trunk (5.7%). 17.1% of patients reported experiencing swelling symptoms over the whole body. On the face, angioedema occurred in 68.6% of patients: the areas around the eyes were affected in 67.1% of cases, the lips in 65.7%, the oral mucosa in 12.9%, and the tongue in 11.4%.

In more than half of the cases (59.8%), hives appear every day, in 16.7% several times a week, in 8.8% several times a month, in 10.8% several times a year, and in 3.9% less frequently.

We examined the prevalence of reported comorbid diseases by CU patients, grouping them into 10 disease categories. The data presented in Table 1 summarize the comorbidity profile of CU patients. Of 102 CU patients, 85.3% had one or more concomitant diseases. Almost 50% of patients had at least one atopic disease or allergy and it was the most
commonly reported group of comorbidities, followed by chronic inflammation and infections (36.3%), thyroid disorders (36.3%), psychiatric disorders (36.3%), skin diseases (18.6%), gastrointestinal diseases (18.6%), cardiometabolic diseases (10.8%), rheumatic diseases (6.9%), malignancies (2.0%), and others included migraine, endometriosis, pernicious anemia and epilepsy.

Among all comorbidities reported by patients, we determined autoimmune diseases. Of 102 CU patients, 31 (30.4%) had one or more comorbid autoimmune diseases (Table 2). The most prevalent were autoimmune thyroid diseases (24.5%, mostly HT in 22.5%). Other common autoimmune comorbidities included systemic lupus erythematosus (2.9%) and rheumatoid arthritis (2.9%). Of the 31 CU patients with a comorbid autoimmune disease, 74.2% had one, most often HT, 22.6% had 2, and 3.2% had 3 (Table 2). As compared to the patients without autoimmune urticaria, many more with autoimmune urticaria had a coexisting autoimmune disease (50% vs. 23.7%).

Interestingly, in 43 patients (42.2%) with CU there was a familial history of autoimmune disease, in 26 patients (25.5%) familial history of atopy, and in 8 patients (7.8%) familial history of chronic urticaria.

Discussion

In line with the findings of previous studies, CSU occurs with a higher frequency than CIndU, with comorbid CIndU likely in a fifth of the cases, despite heterogeneity in the regional distribution of CU and its phenotypes [8]. Symptomatic dermographism has previously been reported to be the most common of the physical urticarias [9]. We observed that delayed pressure urticaria was the most commonly diagnosed CIndU subtype.
### Table 1. The Comorbidity Profile of Chronic Urticaria Patients.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Prevalence in all CU patients (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atopy and allergies</strong></td>
<td></td>
</tr>
<tr>
<td>Drug allergy</td>
<td>21,6%</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>20,6%</td>
</tr>
<tr>
<td>Food allergy</td>
<td>17,6%</td>
</tr>
<tr>
<td>Asthma</td>
<td>15,7%</td>
</tr>
<tr>
<td>Inhaled allergy</td>
<td>12,7%</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>10,8%</td>
</tr>
<tr>
<td>Rhino-conjunctivitis</td>
<td>6,9%</td>
</tr>
<tr>
<td>Insect venom allergy</td>
<td>6,9%</td>
</tr>
<tr>
<td><strong>Chronic inflammation and infectious</strong></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>17,6%</td>
</tr>
<tr>
<td>Gastritis</td>
<td>10,8%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7,8%</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>6,9%</td>
</tr>
<tr>
<td>Periodontitis</td>
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</tr>
<tr>
<td>Otitis media</td>
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<tr>
<td>Hepatitis B</td>
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</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1,0%</td>
</tr>
<tr>
<td><strong>Thyroid disorders</strong></td>
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<tr>
<td>Hashimoto’s disease</td>
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</tr>
<tr>
<td>Hypothyroidism</td>
<td>17,6%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2,9%</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>2,0%</td>
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<tr>
<td>Goiter</td>
<td>1,0%</td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
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<tr>
<td>Depression</td>
<td>16,7%</td>
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<td>Anxiety disorders</td>
<td>14,7%</td>
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<tr>
<td><strong>Skin diseases</strong></td>
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<tr>
<td>Allergic contact dermatitis</td>
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<tr>
<td>Psoriasis</td>
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<td>Vitiligo</td>
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<td>Seborrheic dermatitis</td>
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<td>Alopecia areata</td>
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<td><strong>Gastrointestinal diseases</strong></td>
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<tr>
<td>GERD</td>
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<tr>
<td>IBS</td>
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<td>Peptic ulcer</td>
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<td><strong>Cardiometabolic diseases</strong></td>
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<td>Arterial hypertension</td>
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<tr>
<td>Ischemic stroke</td>
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<tr>
<td>Diabetes mellitus type 2</td>
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<tr>
<td><strong>Connective tissue diseases</strong></td>
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<tr>
<td>SLE</td>
<td>2,9%</td>
</tr>
<tr>
<td>RA</td>
<td>2,9%</td>
</tr>
<tr>
<td>MCTD</td>
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<td>Polymyositis</td>
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<tr>
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<tr>
<td>Carcinoid tumor</td>
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<tr>
<td><strong>Others</strong></td>
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<tr>
<td>Migraine</td>
<td>12,7%</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>5,9%</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>2,0%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1,0%</td>
</tr>
</tbody>
</table>

CU = chronic urticaria; GERD = gastroesophageal reflux disease; IBS = irritable bowel syndrome; MCTD = mixed connective tissue disorder; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.
Table 2. The Number and Combination of Autoimmune Diseases in Chronic Urticaria Patients.

<table>
<thead>
<tr>
<th>AID, No.</th>
<th>Prevalence in all CU patients with AID (n=31)</th>
<th>Prevalence in all CU patients (n=102)</th>
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<tr>
<td>Hashimoto’s disease, 23</td>
<td>74.2%</td>
<td>22.5%</td>
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<tr>
<td>SLE, 3</td>
<td>9.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>RA, 3</td>
<td>9.7%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Vitiligo, 2</td>
<td>6.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Graves’ disease, 2</td>
<td>6.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Pernicious anemia, 2</td>
<td>6.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Autoimmune hepatitis, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Celiac disease, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Alopecia areata, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>MCTD, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Polymyositis, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Number of AID in CU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One, 23</td>
<td>74.2%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Two, 7</td>
<td>22.6%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Three, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Combination of CU of two or more autoimmune diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT + pernicious anemia, 2</td>
<td>6.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>HT + celiac disease, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>HT + vitiligo, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>HT + RA, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>HT + SLE, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>HT + SLE + RA, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>alopecia areata + SLE, 1</td>
<td>3.2%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

AID = autoimmune diseases; CU = chronic urticaria; HT = Hashimoto’s disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

The available data suggest that 33–67% of all patients with CU have concomitant angioedema [10]. We obtained very similar results. Angioedema usually affects the skin on the face, mainly the lips and eyelids [11]. In contrast, our results showed that non-facial body areas were the most frequent locations for angioedema, which may be related to the relatively high percentage of patients with delayed pressure urticaria in our study, which is characterized by erythematous swelling of the skin 4 to 6 hours after the application of pressure. The swelling of the hands and feet provoked by pressure may be difficult to tell apart from swelling caused by angioedema [12].

Most publications do not provide information on the frequency of episodes of CU. The data mainly relate to the duration of the disease, which is estimated at generally 1-5 years [10]. The frequency of urticaria symptoms in this study was estimated as: 59.8% daily, 16.7% several times a week, 8.8% several times a month, and 14.7% irregularly.

Many researchers analyzed mainly allergic diseases accompanying urticaria. Shalom et al. [13] reported that the most common were allergic rhinitis (19.9%) and asthma (10.8%). Zuberbier et al. [14] also concluded that atopy, mainly allergic rhinitis (41.9%), and atopic dermatitis (18.9%) were the most common. A Korean study also highlighted the high burden of allergic rhinitis, drug allergies, and asthma [15]. In the Scandinavian AWARE study, a follow-up study of patients with CU refractory to antihistamine treatment, the most common comorbidities were atopic diseases including asthma, allergic rhinitis, food allergies, and atopic dermatitis. [16]. Our results are similar to these past findings. Type-I auto-allergic CSU is quite common and possibly more likely associated with atopic comorbidities than type- IIb auto-immune driven CSU, which seemingly be the reason for the high frequency of atopic comorbidities observed in the overall CU population [17].

On the other hand, the large registry study from Germany demonstrated hypertensive diseases (43.5%), lipoprotein metabolism disorders (32.1%), and affective disorders (26.0%) as the most frequently reported comorbidities of
Thyroid dysfunctions, especially autoimmunity, have been most commonly found among CU patients, with the reported prevalence ranging up to 60%. Anxiety, depression, and somatof orm disorders have been reported to be the most prevalent mental disorders in CU patients [21]. In our study, almost 26% of patients reported psychiatric disorders, most often depression.

Many authors emphasize the possible role of parasitic infestations and inflammation in chronic urticaria [22]. In our analysis, none of the respondents reported parasitic infestations. Whereas among inflammatory diseases, the most common were sinusitis (17.6%), gastritis (10.8%), and urinary tract infection (7.8%). Authors from Taiwan found peptic ulcer was the most prevalent inflammatory disease (4.83%), followed by hepatitis B/hepatitis C (1.64%) and periodontitis (2.82%) [20].

The association between CU and neoplasm diseases is still controversial. One population-based study reported no association between CU and cancer [23]. A study from Taiwan demonstrated an increased risk of hematological malignant tumors, especially non-Hodgkin lymphoma, in patients with CU [24]. A Korean study showed an increased risk of non-hematological tumors, especially stomach, thyroid, and liver cancers in the case of CU, and thyroid, liver, and prostate cancers in the case of CSU [15]. In our study, two patients reported the presence of melanoma and carcinoid tumor.

A systematic review of the literature on autoimmune comorbidities in patients with CU showed that the most common autoimmune comorbidities were autoimmune thyroid diseases and vitiligo [25]. Our results are similar, except that the next most common diseases after autoimmune thyroid diseases (24.5%) were rheumatoid arthritis (2.9%) and systemic lupus erythematosus (2.9%).

Thyroid dysfunctions, especially autoimmunity, have been most commonly found among CU patients, with the reported prevalence ranging up to more than 50% depending on the inclusion criteria. Association studies using the presence of anti-thyroid antibodies as the criteria usually obtained higher frequencies [26]. In this study, we defined the presence of thyroid disorders based on self-reports by patients. We found the prevalence of thyroid diseases among CU patients was about 36.3%. Hashimoto’s thyroiditis was the most prevalent thyroid disease (22.5%), followed by hypothyroidism (17.6%), hyperthyroidism (2.9%), and Graves’ disease (2.0%).

The relationship of CU with autoimmune thyroid diseases has been underlined for many years and a large number of studies have been conducted worldwide [27]. It is worth noting that most of the studies have analyzed the relationship between CU and thyroid autoimmunity. Little is known about whether CIndU is also linked to thyroid autoimmunity. Our data showed that 26.3% of patients with isolated CU had autoimmune thyroid disease, while with isolated CIndU only 13.6%.

The guidelines of the EAACI/GA2LEN/EDF/WAO recommend that physicians assess CU patients for family history of urticaria and atopy [1]. In our study, family history of urticaria and atopy was negative in the majority of patients, 92.2% in urticaria and 74.5% in atopy. On the other hand, autoimmune disorders were common in family members.

Our study has some limitations. First, respondents were recruited through Facebook groups and there is a potential sample selection bias. Our study population cannot be representative of all chronic urticaria patients as the participation of men has been unrepresentative. We did not use any instrument for assessing urticaria severity therefore we do not know the severity of the disease in the respondents. However, patients participating in urticaria groups typically have more severe and uncontrolled symptoms of the disease. In addition, women participate more actively in social networks and are looking for more information about the diseases they suffer from. Another limitation is the fact that middle-aged patients are more likely to participate actively in social networks and online survey studies thus the obtained data may not be representative of all age groups. Most of our study population were patients between the ages of 19 and 39. Taking into account all of this, our data have over-represented young women and those who have more severe chronic urticaria.

As mentioned above, young women and patients with severe diseases seek more information about the disease they suffer from and are more active on social media. Such a profile of patients participating in our study may affect the percentage of comorbidities which is relatively high compared to other reported publications.

Finally, the high registration percentage of delayed pressure urticaria in our study may be a result of the percentage of angioedema. Regarding the fact that it can be difficult for patients to distinguish between swelling caused by pressure from swelling caused by angioedema they often confuse the two entities or report them in the same way.
Conclusions

In conclusion, CU significantly influences the quality of patients’ lives, which may be negatively affected by the association with a wide range of comorbidities. Our study found that the most common comorbidities in CU include atopic and allergic diseases, chronic inflammations, thyroid, and psychiatric disorders. This pattern of comorbidities seems to be specific to CU. Our data suggest that patients with autoimmune urticaria are more likely to have autoimmune comorbidities than patients without this subtype of CSU. This may be explained by the known co-occurrence of multiple autoimmune phenomena and autoimmune diseases. Therefore, autoimmune comorbidities in patients with chronic urticaria may suggest the presence of a autoimmuneological subtype of CSU, which is usually more severe and has a significantly worse response to omalizumab treatment [28]. Knowledge of the comorbidities of CU may support clinicians in appropriately managing and treating this condition.

Acknowledgments

We would like to express our gratitude to the patients who complete our survey.

References


Comparative Evaluation of Dermatological Emergency Consultations in the Coronavirus Pandemic Era: Tertiary Clinic Experience

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Key words: covid, consultation, emergency, dermatology

Citation: Temel B, Orenay OM, Karaosmanoglu N. Comparative evaluation of dermatological emergency consultations in the coronavirus pandemic era: Tertiary clinic experience. Dermatol Pract Concept. 2023;13(1):e20230112. DOI: https://doi.org/10.5826/dpc.1301a112

Accepted: June 16, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Due to the increase in COVID-19 patients during the pandemic, the workload of emergency departments has increased. The profile of patients seeking non-COVID medical care has changed significantly because of the pandemic; this includes dermatological emergencies.

Objective: The aim was to evaluate and compare adult dermatological emergency consultations during the COVID-19 period with the pre-pandemic period.

Methods: Consulted patients from ED to dermatology between March 11, 2019, and March 11, 2021 were included (Pre-pandemic and pandemic). Age, gender, zone of triage, consultation hour, consultation date, consultation response time, ICD-10 codes were recorded.

Results: The total number of consultations was 639. The mean age of the patients was 44.4 in the pre-pandemic period and 46.1 in the pandemic period. The mean consultation response time was 44.4 minutes in the pre-pandemic period and 60.3 minutes in the pandemic. In the pre-pandemic period, the most common consulted diseases were herpes zoster, urticaria, and allergic contact dermatitis. During the pandemic, the most common consulted diseases were herpes zoster, other dermatitis, and urticaria. There was a statistically significant difference in the incidence of other dermatitis, impetigo/folliculitis, cutaneous vasculitis, and pruritus (p<0.05)

Conclusions: Emergency departments are the busiest and fastest areas of the hospital. Pandemics such as COVID-19 may also occur in the coming years. Informing society about dermatological emergencies and adding adequate dermatology training to the training of emergency physicians will facilitate appropriate patient management in emergency departments.
Introduction

On March 11, 2020, the World Health Organization declared the Coronavirus disease 19 (COVID-19) outbreak as a pandemic, reporting more than 118,000 cases and 4,291 deaths in 114 countries [1]. The rapid spread of COVID-19 all over the world hit health systems hard and prompted many countries to take various measures that aimed to limit the spread of the virus and reduce the number of patients and deaths [2]. The health system, which was rebuilt under the influence of the pandemic, affected every medical department including the dermatology and emergency departments (ED). Almost most of the dermatology inpatient services were reserved for COVID-19 patients, and the number of patients in dermatology outpatient clinics was restricted by health authorities to reduce the spread of the virus [3]. Therefore, the number of dermatologic patients who applied to clinics during the pandemic period decreased, and in addition to this decrease, fear of contracting COVID-19 and skin conditions related to COVID-19 (vesicular eruptions, petechial/purpuric rashes, acral lesions, livedoid lesions, urticarial rash, and maculopapular-erythematous rash) changed the profile of faced dermatological diseases [3-5].

During the pandemic, many COVID-19 patients were first evaluated in hospital EDs. Because of this, the workload in ED increased significantly. There have been many studies investigating the impact of the pandemic on the ED. These studies showed that the number of non-COVID-19 patients admitted to the ED decreased and their disease profiles changed [6,7]. Despite these studies, studies on dermatological diseases consulted from emergency services were limited [8,9]. This study aimed to evaluate adult dermatological emergency consultations during the COVID-19 period and to compare them with the pre-pandemic period.

Material and Methods

Study Design, Patient Selection and Variables

Patients who were consulted to the dermatology clinic by the adult emergency department between March 11, 2020, and March 11, 2021 (pandemic period) and the same dates of the previous year (pre-pandemic period) were included in this study. The dividing point for the pre-pandemic and pandemic period was chosen on March 11, 2020, the day when COVID-19 was declared as a pandemic all over the world. This study was conducted in the Dermatology Clinic of Ankara Training and Research Hospital, which is a tertiary clinic in Turkey. Local ethical approval was obtained for this study. Age, gender, zone of triage, consultation hour, consultation date, consultation response time, and International Classification of Diseases, Tenth Revision (ICD-10) codes were recorded from hospital electronic medical records. Zone of triage was determined as green (simple health conditions that present as an outpatient, are stable in general condition and can be treated on an outpatient basis), yellow (conditions with potentially life-threatening, risk of limb loss and significant morbidity) red (conditions that are life-threatening and require a rapid aggressive approach and urgent simultaneous evaluation and treatment). In our center, consultations requested from the adult emergency between 08:00 and 16:00 are evaluated in outpatient clinics. Between 16.00-08.00, a doctor is assigned to the inpatient clinic for consultation. Consultation time was divided into three time periods 08.00-16.00, 16.00-00.00, and 00.00-08.00. The consulted diseases were classified according to ICD-10 codes. These were dermatitis, infection diseases, hypersensitivity diseases, inflammatory diseases, autoimmune bullous disease, and others. The subgroup disease profile was also determined under these headings one by one. Bullous disorders with extensive involvement, angioedema, erythroderma, toxic epidermal necrolysis, Steven Johnson’s syndrome, pustular psoriasis with metabolic complications were accepted as true dermatological emergencies [10]. These data were evaluated and compared according to pre-pandemic and pandemic periods retrospectively.

Statistical Analysis

Research data was evaluated via Statistical Package for the Social Sciences (SPSS,22, IBM SPSS Statistics for Windows, Version 22.0. Armonk, New York: IBM Corp.). Descriptive statistics were recorded as mean (±) standard deviation, frequency distribution, and percentage. Normality analyses of the data were carried out with the Shapiro-Wilk test. For categorical variables, whether there is a difference in frequency between groups was compared using Pearson chi-square. The t-test was used to evaluate normally distributed means. Mann-Whitney U test was used to evaluate not normally distributed means. The statistical significance value of this study was accepted as p<0.05.

Results

Main Characteristics of Pre-Pandemic and Pandemic Period Consultations

The total number of consultations during the pre-pandemic and pandemic period was 639. It was determined that 467 consultations were requested in the pre-pandemic 1-year period, while 172 consultations were requested in the pandemic 1-year period. It was found that consultations decreased by 63.1% during the pandemic period. The mean age of the patients in the pre-pandemic period was calculated as 44.4±18.6. In the pandemic period, the mean age was calculated as 46.1±18.2. There was no statistically significant difference between the periods in terms of mean age (p=0.31)
(Table 1). 47.3% (n=221) of the patients evaluated in the pre-pandemic period were male and 52.7% (n=246) were female. During the pandemic period, 51.2% (n=88) were men and 48.8% (n=84) were women. There was no statistically significant difference in terms of gender (p=0.38) (Table 1).

In the pre-pandemic period, 40.3% (n=18) of the consultations were requested from the green zone, 50.7% (n=237) from the yellow zone and 9% (n=42) from the red zone. In the pandemic period, 25% (n=43) were requested from the green zone, 64.5% (n=111) from the yellow zone and 10.5% (n=18) from the red zone. There was a statistically significant difference between the periods in terms of gender (p=0.38) (Table 1).

In the pre-pandemic period, 40.3% (n=187) of the consultations were requested between 08.00-16.00, 51.2% (n=239) between 16.00-00.00 and 8.8% (n=41) between 00.00-08.00. In the pandemic period, 45.9% (n=79) of the consultations were requested between 08.00-16.00, 41.3% (n=71) between 16.00-00.00 and 12.8% (n=22) between 00.00-08.00. There was a statistically significant difference between the periods in terms of consultation response time (p=0.04) (Table 1). The mean consultation response time in the pre-pandemic period was 44.4 minutes. It was 60.3 minutes during the pandemic period. There was a statistically significant difference between the periods in terms of consultation response time (p=0.52) (Table 1). 6 (1.3%) of the patients in the pre-pandemic period and 1 (0.6%) of the patients in the pandemic period were hospitalized. There was no statistically significant difference between the periods in terms of hospitalization rates (p=0.34) (Table 1). In the pre-pandemic period, consultation was most requested in August 2019 (n=55) and least in September 2019 (n=25). During the pandemic period, consultation was most requested in July 2020 (n=35) and least in January 2021 (n=2) (Figure 1).

### Comparison of Pre-Pandemic and Pandemic Period Disease Profiles

In the pre-pandemic period, the three most commonly consulted diseases were herpes zoster, urticaria, and allergic contact dermatitis. In the pandemic period, the three most consulted diseases were herpes zoster, other dermatitis, and urticaria. There was a statistically significant difference between the periods in terms of the incidence of other dermatitis, impetigo/folliculitis, cutaneous vasculitis, and pruritus (p=0.01, 0.02, 0.03, 0.01) (Table 2). True dermatological emergencies were detected in 37 (7.9%) patients in the pre-pandemic period and 13 (7.6%) patients in the pandemic period. There was no statistically significant difference between the periods in terms of dermatological emergencies (p=0.86) (Table 1).

### Discussion

The COVID-19 pandemic has deeply affected the health system of every country. During the pandemic period, emergency departments became the first points of contact for COVID-19 patients. Therefore, the number and profile of non-COVID-19 patients admitted to the emergency department changed. In this study, the dermatology consultations requested from the adult emergency department during the pandemic period were examined and compared with the pre-pandemic period.

### Table 1. Characteristics of study.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Pandemic (n=467)</th>
<th>Pandemic (n=172)</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ±Std</td>
<td>44.4±18.6</td>
<td>46.1±18.2</td>
<td>0.31*</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221 (47.3)</td>
<td>88 (51.2)</td>
<td>0.38**</td>
</tr>
<tr>
<td>Female</td>
<td>246 (52.7)</td>
<td>84 (48.8)</td>
<td></td>
</tr>
<tr>
<td>Triage Zones, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green</td>
<td>118 (40.3)a</td>
<td>43 (25)b</td>
<td>0.01**</td>
</tr>
<tr>
<td>Yellow</td>
<td>237 (50.7)a</td>
<td>111 (64.5)b</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Red</td>
<td>42 (9)a</td>
<td>18 (10.5)a</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Consultation time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>08.00-16.00</td>
<td>187 (40)a</td>
<td>79 (45.9)a</td>
<td>0.44**</td>
</tr>
<tr>
<td>16.00-00.00</td>
<td>239 (51.2)a</td>
<td>71 (41.3)b</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>00.00-08.00</td>
<td>41 (8.8)a</td>
<td>22 (12.8)a</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Consultation response time, min</td>
<td>44.4</td>
<td>60.3</td>
<td>0.52***</td>
</tr>
<tr>
<td>Hospitalization, n(%)</td>
<td>6 (1.3)</td>
<td>1 (0.6)</td>
<td>0.34*</td>
</tr>
<tr>
<td>True Dermatological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency,n (%)</td>
<td>37 (7.9)</td>
<td>13 (7.6)</td>
<td>0.86*</td>
</tr>
</tbody>
</table>

Std: Standart Deviation, min: minute, *: T-test, **: Chi-square test, ***: Mann Whitney Utseta,b: Each subscript letter denotes a subset of pandemic status categories whose column proportions do not differ significantly from each other at the 0.5 levels.
Figure 1. Distribution of the Number of Patients by Month.

Table 2. Comparison of Diseases Profile.

<table>
<thead>
<tr>
<th>Diseases, n (%)</th>
<th>Pre-Pandemic</th>
<th>Pandemic</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis, Allergic contact dermatitis, others</td>
<td>73 (15.6)</td>
<td>35 (20.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>Irritant contact dermatitis</td>
<td>13 (2.8)</td>
<td>4 (2.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>39 (8.4)</td>
<td>8 (4.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>Dermatitis, others</td>
<td>21 (4.5)</td>
<td>23 (13.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Infection Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impetigo/folliculitis</td>
<td>223 (47.7)</td>
<td>84 (48.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>28 (6)</td>
<td>3 (1.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dermatophytosis</td>
<td>25 (5.4)</td>
<td>13 (7.6)</td>
<td>0.29</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>12 (2.6)</td>
<td>5 (2.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>8 (1.7)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>125 (20.8)</td>
<td>50 (29.1)</td>
<td>0.56</td>
</tr>
<tr>
<td>Scabies</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Syphilis</td>
<td>22 (4.7)</td>
<td>12 (7)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypersensitivity Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>115 (24.6)</td>
<td>42 (24.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Angioedema</td>
<td>53 (11.3)</td>
<td>16 (9.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Insect Bite</td>
<td>29 (6.2)</td>
<td>13 (7.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>Maculopapular Drug Eruption</td>
<td>11 (2.4)</td>
<td>7 (4.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Erythema Multiforme Y0896</td>
<td>14 (3)</td>
<td>6 (3.5)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>8 (1.7)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Inflammatory Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis Pityriasis Rosea</td>
<td>25 (5.3)</td>
<td>8 (4.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Psoriasis Pityriasis Rosea</td>
<td>8 (1.7)</td>
<td>1 (0.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cutaneous Vasculitis Behcet Disease</td>
<td>10 (2.1)</td>
<td>1 (0.6)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>5 (1.1)</td>
<td>6 (3.5)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Autoimmune Bullous Disease</td>
<td>8 (1.7)</td>
<td>0 (0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Others</td>
<td>23 (4.9)</td>
<td>2 (1.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Alopecia Areata Acne Vulgaris</td>
<td>1 (0.2)</td>
<td>2 (1.2)</td>
<td>0.12</td>
</tr>
<tr>
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<tr>
<td></td>
<td>17 (3.6)</td>
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<tr>
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<td>467 (100)</td>
<td>172 (100)</td>
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* Chi-square test
There were numerous published studies evaluating dermatologic emergency consultations in the pre-pandemic period. The mean age of the patients included in these studies was between 43-51. The rate of male patients was between 47-62% [11-15]. As expected, similar findings were found in the pre-pandemic period of our study.

In pre-pandemic period studies, the most frequently consulted diseases were non-specific dermatitis, scabies, contact dermatitis, herpes zoster, superficial fungal infections, maculopapular drug eruptions, urticaria, erysipelas cellulitis and cutaneous vasculitis [11-15]. However, the incidence of the aforementioned diseases varied in these studies. Similar diseases were also consulted in the pre-pandemic period of our study.

Bullous disorders with extensive involvement, angioedema, erythroderma, toxic epidermal necrolysis, Steven Johnson’s syndrome, pustular psoriasis with metabolic complications were defined as a true dermatological emergency in Gupta et al’s study [10]. On the other hand, Murr et al. defined diseases that started or flared up for 5 days as dermatological emergencies [16]. In pre-pandemic period studies, similar to our results, true dermatological emergencies were between 6-24.7% of the consulted diseases [11,12,15]. It was clearly seen that the rate of real dermatological emergencies among the diseases consulted from the emergency department to dermatology was quite low. We thought that this situation was caused by the fact that public and emergency physicians did not know which dermatological disease was a true emergency.

There were few studies investigating the impact of the COVID-19 pandemic on dermatology consultations requested from emergency departments [8,9]. These studies showed that the number and mean age of consulted patients decreased and the rate of male patients increased during the pandemic period [8,9]. However, our study showed that the mean age of the patients during the pandemic period was higher. On the other hand, Demirel Ogut et al. [8] reported that the rate of hospitalizations and true dermatological emergencies decreased during the pandemic period. Similar results were obtained in our study. Emergency department triage systems facilitate the categorization of emergency patients according to their disease severity and determine both treatment priority and treatment location [17]. In our study, while the rate of patients consulted from the yellow zone increased during the pandemic period, the rate of patients consulted from the green zone decreased. This showed that the number of unnecessary consultations decreased during the pandemic period. We thought that these situations were caused by the fear of infection and the curfews.

In this study, consultations requested between 08.00-16.00 increased and the consultations requested between 16.00-00.00 decreased during the pandemic period compared to the pre-pandemic period. Similar results were obtained by Neslihan Ogut et al. [8]. During the COVID-19 pandemic, countries started to take measures quickly, the most important of which was the curfew. The curfew was imposed on all weekends and weekdays between 21.00-05.00 in our country. We thought that this situation caused a change in consultation hours.

Emergency departments are one of the most crowded places in hospitals that work 7 days and 24 hours. Turkey has the world’s highest number of emergency department visits annually: some 100 million. The high number of patients, especially in our country, is one of the risk factors for transmission during the COVID-19 pandemic. In our study, it was found that consultation response time increased during the pandemic period compared to the pre-pandemic period (44.4 minutes vs 60.3 minutes). Both the working of dermatology physicians in the COVID departments and the increase of COVID patient load on emergency departments should have increased the consultation response time. The prolongation of the consultation response time increased the length of stay of the patients in emergency departments and this situation could have increased the non-COVID patient burden on emergency departments.

Along with the pandemic, the distribution of the number of patients by month also changed. Demirel Ogut et al. [8] reported that the number of patients decreased in March 2020, April 2020, and May 2020 compared to 2019, and the number of patients started to increase as of June 2020. A similar trend was obtained in our study. Interestingly, in our study, the number of patients decreased as of July 2020, and the number of patients in 2019 could never be reached. In our country, full or partial curfews were implemented to coincide with the periods when the number of patients decreased. We thought that this result was caused by the curfews and travel bans during the pandemic period.

Pandemic period studies showed that the profile of the disease consulted from emergency departments has changed [8,9]. In Isoletta et al.’s study, although urticaria, atopic eczema and acute onset infections were reported to be the most frequently consulted diseases during the pandemic period, urticaria, vasculopathic lesions and scabies were found to be statistically significantly higher compared to the pre-pandemic period [9]. In Demirel Ogut et al’s study, although contact dermatitis, scabies and urticaria were reported to be the most frequently consulted diseases during the pandemic period, scabies and pityriasis rosea were found to be statistically significantly higher and herpes zoster was found statistically significantly lower compared to the pre-pandemic period [8]. In addition to obtaining similar results, the rate of pruritus and impetigo/folliculitis was statistically significantly lower in our study. These results showed that non-urgent situations decreased during the pandemic period.
period. In our study, as in other studies [8, 9], diseases previously associated with COVID-19 disease and vaccines such as herpes zoster, cutaneous vasculitis and urticaria were listed. Emergency department physicians should be careful about these diseases and COVID-19 should be investigated.

Limitations
This study had some limitations. The study was retrospectively planned from a single care center. The diagnoses of the patients were made according to ICD-10 codes. There may have been person-based errors in adding the diagnostic codes to the system. More than one doctor was evaluating the consultations. In this case, there may be conflicts about the accuracy of the diagnoses. However, to correct this situation, the diagnosis is confirmed by a second doctor.

Conclusion
This study showed that the prolongation of the consultation response time increased during the COVID-19 pandemic period. The distribution of the number of patients by month changed, and the number of patients decreased as of July 2020. The profile of dermatological diseases consulted from the emergency department also has changed. During the pandemic period, non-urgent conditions such as impetigo/folliculitis and pruritus decreased. Emergency departments are the busiest and fastest areas of the hospital. Pandemics such as COVID-19 may also occur in the coming years. Informing the public about dermatological emergencies and adding adequate dermatology training to the training of emergency physicians will facilitate appropriate patient management in emergency departments.

References
Follow-up of Favipiravir-Induced Nail Fluorescence: Implications for Nail and Drugs

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Key words: favipiravir, nail, fluorescence, drug

Introduction: Favipiravir creates fluorescence on nails, which can be seen with Wood's light.

Objectives: The objectives of this study are to examine the properties of fluorescence in the nail due to favipiravir and to observe whether other drugs also produce fluorescence in the nail.

Methods: The research is descriptive, prospective, and quantitative. This study recruited 30 healthcare workers who received favipiravir treatment and 30 volunteers who took or did not take any medication except favipiravir from March 2021 to December 2021. Fingernails of the patients and control groups were examined under Wood's light in the darkroom. If fluorescence was observed in the fingernails, we followed up once a month until the fluorescence disappeared. We calculated the nail growth rate by dividing the distance of nail fluorescence from the proximal nail fold by the number of days since favipiravir was started.

Results: We found nail fluorescence in all patients receiving a loading dose of favipiravir. The fluorescence in the nail decreased and disappeared in the 3rd month. The average nail growth rate at the first visit was 0.14 mm/day. The nail growth rate at the second visit was 0.10 mm/day. A statistically significant difference was found between the first and second visit nail growth rates (z: -2.576; p=0.010<0.05). We found that other drugs did not produce any fluorescence in the nail.

Conclusions: Nail fluorescence induced by favipiravir is dose-dependent and decreases in intensity over time. Nail fluorescence due to favipiravir is likely due to the active ingredient of the drug.
Introduction

The human eye can only process visible light (400–720 nm), which is a narrow segment of the electromagnetic spectrum (EMS). Our retina is not capable of sensing light in the UV spectrum (10–400 nm) but can detect longer wavelength fluorescence caused by the interaction of UV light with skin chromophores. Wood’s light is frequently used in dermatology to detect fluorescence produced by exogenous or endogenous chromophores [1].

Favipiravir, a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazine carboxamide), is a broad-spectrum antiviral drug with inhibitory effects on a variety of RNA viruses [2]. Favipiravir is widely used in Turkey to treat coronavirus disease 2019 (Covid-19) based on the Covid-19 treatment guide of the Ministry of Health, Republic of Turkey. A loading dose of 2x1600 mg (first day) of favipiravir followed by 2x600 mg/day (4 days) for a total of 4 days is recommended.

Wood’s lamp is a high-pressure mercury arc lamp filtered with barium silicate and nickel oxide, emitting ultraviolet in the 320–400 nm spectrum with a peak at 365 nm. When examining a Wood’s lamp in a dark room, fluorescence is seen if there are fluorophores [3]. So far, the following fluorescence has been reported in the nail due to drug use: yellow for tetracycline, yellow/green for quinacrine, and yellow/green/blue fluorescence for favipiravir [4-9].

We wanted to follow up on whether nail fluorescence in all patients using favipiravir persisted or not and how long nail fluorescence persists. Data on the fluorescence of drugs in nails are limited to a few drugs. We wanted to collect information about whether other drugs create fluorescence in the nails by including people who use drugs as a control group in our study. We thought that the data we obtained could provide information about drug transfer to the nail and the relation between drugs and nails.

Material and Methods

Patients who received favipiravir treatment due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) positivity diagnosis among healthcare workers at our hospital were included in the study as the study group. Only an observational study was planned, without any interference with patients’ drug doses or treatment duration. The reason for choosing healthcare professionals is to facilitate follow-up and eliminate the risks that may occur due to patients coming to the hospital. In the control group, individuals who did not receive favipiravir treatment and were or were not using another systemic drug were included in the study. The research is descriptive, prospective, and quantitative.

Volunteer adults between the ages of 18–65 were included in the study. An informed consent form was obtained from all participants. Those who were pregnant or breastfeeding were not included in the study. We recorded the age, gender, drug use, vitamin and supplement use of the study and control groups. The drugs taken as a criterion for systemic drug use were taken at least 15 days before and drugs taken for more than 5 days were recorded.

Approval from the Ministry of Health of the Republic of Turkey with the number 2021-01-13T13_41_11 and permission from the ethics committee of Maltepe University with the number 2021/900/19 were obtained.

We conducted this study among 30 healthcare workers who received favipiravir treatment and 30 volunteers who took or did not take any medication between 04/03/2021 and 25/12/2021. The fingernails of the patients and control groups were examined under Wood’s light (Lumio®UV, 3Gen DermLite™, 40 UV LEDs, 75 mm 2x lens, U.S.A.) in the darkroom. If fluorescence was observed in the fingernails, we followed up once a month until the fluorescence disappeared. The length of the third fingernails of the left hand of all patients was measured. The left hand was chosen as it is usually the non-dominant hand and the middle finger because it is easy to position. The cuticle (eponychium) was not included when measuring nail length or fluorescence. We measured the size of the fluorescence in the nail. In addition, the distance of the fluorescence from the distal tip of the nail and the proximal nail fold was also measured. Measurements were made from the midpoint of the nail using a digital caliper (Figure 1). It was not possible to see all of the patients in the 1st month and the 2nd month. 1st month was accepted as 31±3 days, 2nd month was 61±3 days.

The first visit nail growth rate was calculated as mm/day by dividing the distance between the proximal nail fold and the first distal fluorescence by the measurement day. The 2nd visit nail growth rate was obtained by subtracting the distance of the distal fluorescent from the proximal nail fold measured at the 2nd visit from the first measured at the 1st visit and dividing by the number of days in between (Figure 2).

Statistics

Power analysis in the research was carried out with the G Power 3.1.9.7 program. Assuming that the difference between 2 observations will be examined, the t-test family was taken as reference, and the effect size was accepted as 0.8 using the wide Cohen reference since there was no similar prior study. In addition, it was concluded that it would be sufficient to have 15 people in the analysis of the main hypothesis at 80% power and 5% significance levels. Since there were 20 people who could be followed up in the study, the sample size obtained was considered sufficient.

The SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program analyzed the variables. We used the
Pearson chi-square test to examine whether there was a gender difference between the control group and the study group. We examined the distribution of age by skewness and kurtosis (-1 - +1). Accordingly, we examined the ages of the study/control groups with the t-test.

When comparing the elongation rates of the nail fluorescence, the Gaussian distribution was examined and it was found that it was not normal. Accordingly, the Wilcoxon Signed-Rank test was used. Hypothesis tests were performed with the help of the SPSS 22.0 program at a 95% confidence level.

Quantitative variables were expressed as mean (± standard deviation), and median (minimum-maximum), while categorical variables were shown as n (%). The variables were analyzed at a 95% confidence level, and a p-value less than 0.05 was considered significant.

Results
24 (80.0%) of the participants included in the study group were women; 6 of them (20.0%) were male. Their mean age is 36.10±9.03 years. The average length of the left-hand third

Figure 1. Measurement methods (A: Measurement method for the midpoint of the nail fluorescence B: The measurement of the third fingernails of the left hand).

Figure 2. The first (A) and second (B) visit measurement of the nail fluorescence size (Black lines indicate the size of the fluorescence. The red line shows the distance between the distal end of the fluorescence and the proximal nail fold).
the proximal nail in the other (Figure 4). Furthermore, in a patient who received favipiravir twice, examined on the 62nd day of the 1st dose and the 48th day of the 2nd dose, fluorescence was observed in the entire nail (Figure 5).

In the measurements made from the 3rd nail of the left hand, the nail fluorescence of 10 patients could be measured in the 1st month. The mean nail fluorescence length was 3.95±0.67 mm (min-max 3-5) in the first month. The nail fluorescence of 20 patients could be measured in the second month and the mean nail fluorescence length was 4.3±0.77 mm (min-max 2.9-5.9).

The last visits of the patients were between 62-122 days (92.07±11.28). Nail fluorescence intensity gradually decreased in all patients with fluorescence and disappeared completely in the third month.

The first visit nail growth rate could be calculated in 25 patients, and the mean was 0.14 mm/day min-max 0.06-0.22. The second visit nail growth rate could be calculated in 20 patients whose fluorescence measurement could be made in the 2nd-month follow-up, and it was 0.10 mm/day min-max 0.07-0.19. In the analysis comparing the differences between the first and second nail growth rates, a statistical difference was found (z: -2.576; p=0.010<0.05) (Table 3).

Some patients in the study group took additional medications such as valproic acid, lithium carbonate, levohydroxine, olanzapine, mirtazapine, methylphenidate, paroxetine, vitamin D3, zinc, vitamin B1/B2/B6/B12, vitamin C, nicotinamide, biotin, folic acid, paracetamol, enoxaparin, nebivolol, N-acetyl cysteine, magnesium, colchicine, prednisolone, metformin, pantoprazole, phentiramine maleate, amoxicillin/ clavulanic acid, ketoprofen, levocetirizine/monelukast, acetylsalicylic acid, omega 3 and blackberry extract. The

<table>
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<th>SD</th>
<th>t</th>
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<tr>
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<tr>
<td>Left-hand 3rd nail length</td>
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<td>15.70</td>
<td>11.8633</td>
<td>1.85370</td>
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</tr>
</tbody>
</table>

Table 2. Comparison of Study and Control groups according to left-hand 3rd nail length. t: Independent samples t-test value

fingernails is 11.28±0.188. In the control group, 20 (66.7%) of the 30 participants were female, and 10 (33.3%) were male. Their mean age is 37.37±13.12. The average length of the left-hand third fingernails is 11.86±1.85. In total, 44 of 60 participants were women; 16 of them were male. Their mean age is 36.73±11.19 years. The average length of the left-hand third fingernails is 11.57±1.88 (Table 1).

When the study and control groups were compared according to the length of the left-hand third fingernail, no statistically significant difference was found (p>0.05) (Table 2).

In the study group, fluorescence was observed in 27 of 30 patients (90%) using favipiravir. The three patients without fluorescence did not use the total dose of favipiravir. One of these patients vomited after taking eight tablets on the first day, one took only five tablets of favipiravir, and one did not take the loading dose on the first day (Figure 3). Blue fluorescence was observed in the fingernails of all patients who used 2x1600 mg (day 1) of favipiravir, followed by 2x600 mg/day for a total of 4 days.

The earliest evaluation after starting favipiravir was on the 5th day of treatment, and we did not see fluorescence in her nail. 2 patients were evaluated on day eight, and we found fluorescence of 1 mm in one patient and 3.3 mm in the proximal nail in the other (Figure 4). Furthermore, in a patient who received favipiravir twice, examined on the 62nd day of the 1st dose and the 48th day of the 2nd dose, fluorescence was observed in the entire nail (Figure 5).

In the measurements made from the 3rd nail of the left hand, the nail fluorescence of 10 patients could be measured in the 1st month. The mean nail fluorescence length was 3.95±0.67 mm (min-max 3-5) in the first month. The nail fluorescence of 20 patients could be measured in the second month and the mean nail fluorescence length was 4.3±0.77 mm (min-max 2.9-5.9).

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Some patients in the study group took additional medications such as valproic acid, lithium carbonate, levohydroxine, olanzapine, mirtazapine, methylphenidate, paroxetine, vitamin D3, zinc, vitamin B1/B2/B6/B12, vitamin C, nicotinamide, biotin, folic acid, paracetamol, enoxaparin, nebivolol, N-acetyl cysteine, magnesium, colchicine, prednisolone, metformin, pantoprazole, phentiramine maleate, amoxicillin/ clavulanic acid, ketoprofen, levocetirizine/monelukast, acetylsalicylic acid, omega 3 and blackberry extract. The
Figure 3. Patients without nail fluorescence. (A: The patient vomited after taking eight tablets, B: The patient took only five tablets, C: The patient did not take the loading dose of favipiravir.

Figure 4. The earliest evaluation of the nail fluorescence for three patients after starting favipiravir. A: 5th day of treatment, and no fluorescence is visible. B: 8th day of treatment, and 1 mm fluorescence is seen. C: 8th day of treatment and 3.3 mm of fluorescence is observed.)
nail bed. The elongation of fingernails is about 0.1 mm/day and differs between individuals [10]. While aging, acute infections, systemic illness, and malnutrition slow down nail growth, nail growth is faster in those with pregnancy, warmer temperatures, and minor trauma [11]. In the study group, the 1st visit nail growth rate, which represents approximately the 1st month, was found to be significantly higher than the 2nd visit nail growth rate, which approximately represents the 2nd month. The increase in nail growth rate may be related to Covid-19 infection, use of favipiravir, taking vitamins due to illness, or trying to eat better. Since we could not evaluate the nail growth rate in the control group, we cannot comment. Since we could only make the nail growth rate comparison in 20 patients, it is impossible to say this with certainty. In addition, since what we are measuring is fluorescent, the intensity of the light decreases over time, which may have caused inaccuracies in the measurements.

Table 3. Comparison of 1st visit and 2nd visit nail growth rate (N=20).

<table>
<thead>
<tr>
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<th>Mean±SD</th>
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<th>z</th>
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<tbody>
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<td>1st visit nail growth rate</td>
<td>0.14±0.044</td>
<td>0.14 (0.10-0.19)</td>
<td>-2.576</td>
<td>0.010*</td>
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<tr>
<td>2nd visit nail growth rate</td>
<td>0.10±0.034</td>
<td>0.09 (0.08-0.11)</td>
<td>-2.576</td>
<td>0.010*</td>
</tr>
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z: Wilcoxon signed-rank test statistics value; Q₁: 25. percentile; Q₃: 75. percentile; *: p<0.05

fluorescence seen in the nail was consistent with the intake of favipiravir, we did not observe that the above-mentioned drugs affected this fluorescence.

In the control group, the drugs taken by the patients include metformin, nebivolol, sertraline, levothyroxine, drospirenone/ethinylestradiol, desloratadine/montelukast, fluoxetine, budesonide/formoterol, isorretinoin, ibuprofen, ramipril/hydrochlorothiazide, iron/folic acid, terbinafine, perindopril/indapamide, alfuzosin, diltiazem, pregabalin, duloxetine, carvedilol, escitalopram, telmisartan, amlodipine, candesartan, enalapril, ofloxacin, zinc, biotin, and melatonin. Nail fluorescence was not observed in any of the control group patients.

Discussion

The nail plate is composed of layers of keratinized cells produced by the nail matrix and extends distally over the nail bed. The elongation of fingernails is about 0.1 mm/day and differs between individuals [10]. While aging, acute infections, systemic illness, and malnutrition slow down nail growth, nail growth is faster in those with pregnancy, warmer temperatures, and minor trauma [11]. In the study group, the 1st visit nail growth rate, which represents approximately the 1st month, was found to be significantly higher than the 2nd visit nail growth rate, which approximately represents the 2nd month. The increase in nail growth rate may be related to Covid-19 infection, use of favipiravir, taking vitamins due to illness, or trying to eat better. Since we could not evaluate the nail growth rate in the control group, we cannot comment. Since we could only make the nail growth rate comparison in 20 patients, it is impossible to say this with certainty. In addition, since what we are measuring is fluorescent, the intensity of the light decreases over time, which may have caused inaccuracies in the measurements.
The incidence of fluorescence in nails due to the use of favipiravir was previously reported as 81.9% and 84% [9, 12]. Similar to the findings in these studies, we observed fluorescence in the nail in 90% of our patients using favipiravir, and we observed that there was fluorescence in the nail in 100% of the patients who received the full loading dose.

Nail manifestations associated with COVID-19 included a red half-moon sign, transverse orange nail lesions, Mees' lines, and Beau’s lines [13]. No nail disorder was observed in any of our patients who had Covid-19.

Nail fluorescence due to favipiravir was seen in all patients who received the total dose of favipiravir. It was observed that the density decreased in the 2nd month and disappeared in all patients in the 3rd month. Nail fluorescence was not observed in patients who did not receive the loading dose. The fluorescence produced by favipiravir in the nails is dose-dependent and decreases over time. These findings showed that the drug dose is important in drug transfer to the nail.

Drug delivery to the nail is most important in the treatment of onychomycosis. Continuous therapy and intermittent pulse regimens for terbinafine and itraconazole can be used to treat onychomycosis. Similar efficacy and side-effect rates have been reported in a meta-analysis [14]. We evaluated the fluorescence in the nails due to the use of high-dose favipiravir for 5 days in our patients as an opportunity to monitor the transfer of the drug to the nails and how long it took to disappear. And the decrease of this fluorescence over time showed that the drug concentration in the nail did not remain the same, and we did not see any fluorescence in the distal 1/3 of the nail, except in one patient who took favipiravir twice. In onychomycosis, the distal lateral subungual type, in which the distal and lateral parts of the nail are affected, is the most common [15]. We think that insufficient access of antifungal drugs to the micelles located in the distal nail may be an important factor in treatment failure in onychomycosis.

The maximum plasma concentration of favipiravir occurs 2 hours after oral administration and then decreases rapidly with a short half-life of 2-5.5 hours [2]. Itraconazole has plasma half-lives of 42 hours and terbinafine of up to 100 hours [16]. It can be thought that it can affect a much larger area of the nail than favipiravir.

It is not known in what way the use of favipiravir creates fluorescence in the nails. In one study, it was claimed that it could be caused by excipients such as titanium dioxide and yellow ferric oxide added to the favipiravir tablet for photo stabilization due to the “fluoro” in the favipiravir formulation [17, 18]. Pure favipiravir has been shown to exhibit blue fluorescence in microscopic fluorescence examination [19]. In addition, titanium dioxide and yellow ferric oxide were among the additives of the drugs taken by some patients in the patient and control groups, and fluorescence was not observed in the nails due to these drugs in these patients. Based on this information, we think that favipiravir-induced nail fluorescence is mainly caused by the drug rather than the favipiravir tablet additives. However, since these drugs were one-per-day tablets, it would not be correct to compare the dose with 16 tablets a day, as in favipiravir.

Since the nail is in a structure that can indicate long-term exposure to a substance, it is used to evaluate environmental exposure, in the detection of abused drugs and poisoning [20]. It should be taken into account that the substance accumulated in the nail may decrease over time when drug measurement is made in the samples obtained by nail clipping. And although the time the nail is cut varies from person to person, it gives information about 3-4 months prior in the average fingernail.

**Conclusion**

Favipiravir-induced nail fluorescence is dose-dependent, and its intensity decreases over time. We think that the concentration of the drugs in the nails decreases over time. Nail fluorescence due to favipiravir is probably due to the active ingredient in the drug. We think that the information we have obtained may be useful in the treatment of conditions such as onychomycosis where drug transfer to the nail is important and in determining the concentration of nail exposure substances.

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8. Gürleren D, Yalıcı-Armagan B. Yellow-white fluorescence on the nails: A novel finding of Favipiravir used for the treatment


Can Multispectral Dermoscopy Help In Distinguishing Blue Color?

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Key words: dermoscopy, blue naevus, angioma, multispectral, skin parameter maps


Accepted: May 31, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The interpretation of colors is essential in the dermoscopic evaluation of skin lesions. The same blue color on white dermoscopy may indicate blood or pigment deep in the dermis. Contrary to white dermoscopy, multispectral dermoscopy uses different wavelengths of light to illuminate a lesion and is able to decompose the dermoscopic image into individual maps that allow to more clearly visualize specific skin structures such as pigment distribution (pigment map) and vasculature (blood map). These maps are called skin parameter maps.

Objectives: The aim of this research is to investigate whether skin parameter maps can be used to objectively identify and distinguish the presence of pigment and blood, by using blue naevi and angiomas as models for respectively pigment and blood.

Methods: We retrospectively analyzed 24 blue naevi and 79 angiomas. The skin parameter maps of each of the lesions were independently reviewed by 3 expert dermoscopists, in the absence of the regular white-light dermoscopic image.

Results: All the observers provided high levels of diagnostic accuracy for blue naevus and angioma based on skin parameter maps alone, and the dermoscopic diagnosis was considered substantially reliable because of the 79% of diagnostic K agreement. Percentages of blue naevi and angiomas that showed respectively deep pigment and blood were very high at 95.8% and 97.5%. There was a percentage of lesions that counterintuitively showed blood in blue naevi (37.5%) and deep pigment in angiomas (28.8%).
Introduction

The interpretation of colors is essential in the dermoscopic evaluation of skin lesions. These colors result from different chromophores in the skin, such as pigment and blood. Depending on the location of pigment in the skin, white light dermoscopy reveals the following colors: brown (pigment at the dermo-epidermal junction), black (pigment in the stratum corneum or superficial epidermis), gray (pigment in the papillary dermis) or blue (pigment in the reticular dermis). A red, blue or purple color represents blood [1]. Consequently, the same blue color on white dermoscopy may indicate blood or pigment deep in the dermis [2]. In contrast to white light dermoscopy, multispectral dermoscopy uses different wavelengths of light to illuminate a lesion. This technique is able to decompose the dermoscopic image into individual maps that allow to more clearly visualize specific skin structures such as pigment distribution (pigment map) and vasculature (blood map). These visualizations can be generated in real-time and are called skin parameter maps (SPM) [3]. A further distinction between superficial and deep pigment can be made, based on their different spectral signature, which can be visualized with a superficial and deep pigment map.

Objectives

The aim of this research is to investigate whether skin parameter maps can be used to objectively identify and distinguish the presence of pigment and blood. We conducted a retrospective study on blue naevi and angiomas as prototypes of lesions with, respectively, pigment deep in the dermis (melanin-producing melanocytes deep in the dermis) and collection of capillaries in the dermis to validate the presence of pigment or blood in skin parameter maps.

Methods

We retrospectively analyzed all dermoscopic images taken of blue naevi and angiomas that were collected in two centers (UZ Leuven and UZ Gent) from February 2019 until January 2020 using a handheld digital dermatoscope (Barco Demetra®), after patients had given informed consent. Diagnosis was either histopathologically proven or made clinically (by LJ or SM). This study was conducted in accordance with good clinical practice guidelines. The research protocol was approved by the Ethics Committee of Leuven (s60193). A deep pigment and blood parameter map was created for all the lesions, aiming to highlight respectively the presence of deep pigment or blood. These two skin parameter maps of each lesion were independently reviewed by 3 expert dermoscopists (EV, LB and MG).

Setting

The images of the skin parameter maps (deep pigment and blood) were presented in a mixed order to the observers and scored blinded to the white light dermoscopic image or diagnosis and without knowledge of any clinical data. In each case, the presence of deep pigment and blood was semiquantitatively scored as absent or present. Additionally, participants were asked to diagnose the lesion (blue naevus or angioma) based on the multispectral images alone and to assess in which of the two skin parameter maps the signal was highlighting most.

Outcomes

The primary outcome measure was the rate of lesions in which a signal in the blood and/or pigment map was observed. Secondary outcomes were correlation of intensity with a correct diagnosis, interobserver concordance and the accuracy rate in predicting angioma versus blue naevus.

Statistical Analysis

The prevalence of pigment or blood was compared among the 2 lesion groups (blue naevus, angioma) using the $\chi^2$ test. All P values cited are two-sided, and values of P less than .05 were considered statistically significant. Sensitivity and specificity for the diagnosis of the skin lesions were calculated for each observer as compared to clinical or histopathologic diagnosis. The agreement between ratings made by 3 expert dermoscopists (interrater reliability) was estimated using Fleiss’ kappa statistic with 95% confidence intervals. Statistical analysis was performed with SPSS statistics for Windows version 26 (IBM Corp).

Results

Images of 103 lesions, of which 24 blue naevi and 79 angiomas, were collected. Ten lesions (6 blue naevi and 4 angiomas) were histologically confirmed. For the other lesions,
the diagnosis was made clinically (by LJ or SM). An example of skin parameter maps as shown to the observers is shown in Figure 1. Out of the 24 blue naevi, 23 showed a signal on the deep pigment map (95.8%), whereas in only 22 out of the 79 angiomas (28.8%) a signal on the deep pigment map was observed ($p<0.001$). In 77 out of 79 angiomas (97.5%) a signal was detected in the blood map, versus 9/24 (37.5%) in blue naevi ($p<0.001$) (Table 1).

Next, we checked if the intensity of the signal of the skin parameter map correlates with the correct diagnosis. When choosing the most intense signal between the two skin parameter maps, we found that in 20 out of the 24 blue naevi (83.3%) the intensity of the signal was most pronounced in the deep pigment map. Of 79 angiomas, in 72 of them (91.1%) the most intense signal was seen in the blood map. To determine if there was agreement between the answers of the three experts a Fleiss' kappa was made. Overall, there was good agreement, $\kappa = .792$ (95% CI, .790 to .793). 84.5% of all questions (presence or absence of deep pigment or blood, most highlighted skin parameter map and diagnosis) were answered unanimously by the three experts. In the other 15.6% of cases, majority decision-making was used. As far as diagnosing blue naevi and angiomas based on the skin parameter maps alone, a sensitivity of 81% (64 out of 79 angiomas diagnosed correctly) and a specificity of 100% (24 out of 24 blue naevi diagnosed correctly) with an overall accuracy of 85.4% was reached. Of the 15 cases that were diagnosed incorrectly, 7 of them were not answered unanimously by the observers.

An illustration of blood and deep pigment maps of two blue naevi and an angioma, in addition to the information from regular white dermoscopy (which was not shown to the observers), is shown in Figure 2. In the skin parameter maps of Image A, only pigment is highlighted, as expected in a blue naevus. In Image B, a collision between a blue naevus and angioma, the angioma is highlighted in the blood contrast map, whereas the blue naevus is highlighted in the pigment contrast map. These two cases illustrate the possible use of these skin parameter maps to diagnose skin lesions. The use of skin parameter maps may not only be limited to blue naevi and angiomas, but could be useful in other types of skin lesions (e.g. basal cell carcinoma).

![Figure 1. Skin parameter maps (left deep pigment map, right blood map) of a blue naevus (top row) and angioma (bottom row).](image)

<table>
<thead>
<tr>
<th>Table 1. Absolute and relative frequencies of presence of deep pigment and blood in the skin parameter maps of blue naevi and angiomas.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin parameter map</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Deep pigment</td>
</tr>
<tr>
<td>Blood</td>
</tr>
</tbody>
</table>
skin parameter maps could help to determine if the lesion is a vascular or pigmented lesion. Despite the fact that it was not an objective to use the skin parameter maps without the corresponding white light image, this research indicates that the sensitivity and specificity are good when using skin parameter maps on their own for these skin lesions. Our recommendation for the application of skin parameter maps in general practice would still be to use them in conjunction with the white light image.

Conclusion

Skin parameter maps based on multispectral images can help to objectify the presence of deep pigment or blood in blue naevi and angiomas. Application of these skin parameter maps could help in the differential diagnosis between pigmented and vascular lesions. These skin parameter maps should be used complementary to regular dermoscopy, but assessment based on the skin parameter maps alone results in good diagnostic accuracy.

References

The Role of Ischemia-modified Albumin and Ischemia-Modified Albumin to Albumin Ratios in Patients with Alopecia Areata

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Key words: alopecia areata, ischemia-modified albumin, IMA/albumin, disease severity

Citation: Tanacan E, Oztekin A, Savcı U, et al. The Role of Ischemia-modified Albumin and Ischemia-modified Albumin to Albumin Ratios in Patients with Alopecia Areata. Dermatol Pract Concept. 2023;13(1):e2023017. DOI: https://doi.org/10.5826/dpc.1301a17

Accepted: September 7, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction:

Objective: To investigate the role of ischemia-modified albumin (IMA) and IMA/albumin levels in patients with AA.

Methods: The present prospective crossectional study includes patients ≥18 who were admitted to the Dermatology and Venerology Department of Hitit University Hospital between April 1, 2021, and September 30, 2021. 70 patients participated in the study (n=34 for the study group and n=36 for the control group). Demographic features, clinical characteristics, IMA, and IMA/albumin levels were compared between the groups. The study group was divided into subgroups based on the number of patches, disease duration, and the number of disease attacks. IMA and IMA/albumin levels were compared between each subgroup.

Results: The study and control groups were similar with regard to demographic features and clinical characteristics. Significant differences were observed between the mean IMA and IMA/albumin ratio (p=0.004 and 0.012, respectively). The study subgroups were comparable in the number of patches, disease duration, and number of disease attacks.

Conclusion: Although oxidative stress is an important component in the etiology of AA, IMA and IMA/albumin may not be useful in the prediction of disease severity in patients with AA.
Introduction

Alopecia areata (AA) is a chronic, immune-mediated disease resulting in non-scarring hair loss with an approximate prevalence of 1/1000 [1]. Hair follicles in the anagen phase prematurely transform into catagen and telogen phases by autoimmune and inflammatory mechanisms resulting in a sudden hair loss in patients with AA [2]. Although the pathophysiological mechanisms behind AA have not been clearly revealed yet, immune dysregulation, genetic predisposition, and excessive oxidative stress seem to be the main predisposing factors behind the development of AA [3].

Oxidative stress and free radical damage alter the chemical structure of albumin, leading to the production of ischemia-modified albumin (IMA) [4]. Hence, the utility of IMA and IMA/albumin were investigated in various studies for revealing the oxidative stress-related events behind the etiology of autoimmune and inflammatory diseases [5, 6].

The role of IMA was also investigated in several dermatologic diseases like psoriasis, Behçet’s disease, and alopecia areata [7-9]. However, no consensus has been reached on the utility of IMA in daily dermatology practice. For this reason, more data is necessary to reach more precise results.

The aim of the present study is to investigate the role of IMA and IMA/albumin levels in patients with AA.

Material and Methods

The present prospective cross-sectional study consisted of patients ≥18 who were admitted to the Dermatology and Venereology Department of Hitit University Hospital between April 1, 2021, and September 30, 2021. Seventy patients participated in the study (n=34 for the study group and n=36 for the control group). Patients with alopecia areata served as the study group. Thirty-six gender and age-matched patients with dermatologic complaints other than inflammatory skin diseases were used as the control group. Cases with pregnancy, lactation, history of malignancy, and active or chronic infection were excluded from the study. Written informed consent was signed by all participants. The institutional ethics committee approved the study protocol with reference number 449. Firstly, the clinical characteristics of AA patients were evaluated. Gender, pattern of alopecia area, duration of disease, family history with AA, involved area (scalp, beard, eyebrow) and the number of disease attacks were evaluated for each AA patient. Both study and control groups were evaluated for gender, age, height (m), weight (kg), Body mass index (BMI), smoking and alcohol consumption, IMA, and albumin levels. The IMA/albumin ratio of all participants was calculated. Afterwards, the study group was divided into subgroups based on number of patches, disease duration, and number of disease attacks. IMA and IMA/albumin levels were compared between each subgroup. All the blood samples (peripheral venous blood) from all participants were collected after overnight fast. Statistical analyses were performed by Statistical Package for the Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.).

Student t-test was used for comparing the mean values between the groups as the data was normally distributed. Chi-square test was conducted to compare the categorical variables. Pearson correlation test was performed for correlation analyses. A two-tailed P value < 0.05 was regarded as statistically significant.

Results

The clinical characteristics of the patients with Alopecia Areata were shown in Table 1. In the alopecia areata group, most of the participants were male. Approximately 60% of the patients had a single patch. Disease duration was less than one year in 19 patients. Only three patients had a family history of alopecia areata.

Table 1. Demographic features and Disease Characteristics of the patients with Alopecia Areata.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>35.3%</td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>64.7%</td>
</tr>
<tr>
<td>Pattern of AA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single patch</td>
<td>20</td>
<td>58.8%</td>
</tr>
<tr>
<td>Multiple patch</td>
<td>14</td>
<td>41.2%</td>
</tr>
<tr>
<td>Duration of illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>19</td>
<td>55.9%</td>
</tr>
<tr>
<td>1-4 years</td>
<td>9</td>
<td>26.5%</td>
</tr>
<tr>
<td>≥5 years</td>
<td>6</td>
<td>17.6%</td>
</tr>
<tr>
<td>Family history of AA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>8.8%</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>91.2%</td>
</tr>
<tr>
<td>Involvement area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>22</td>
<td>64.7%</td>
</tr>
<tr>
<td>Beard</td>
<td>8</td>
<td>23.5%</td>
</tr>
<tr>
<td>Eyebrow</td>
<td>2</td>
<td>5.9%</td>
</tr>
<tr>
<td>≥2</td>
<td>2</td>
<td>5.9%</td>
</tr>
<tr>
<td>Number of attacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>58.8%</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>29.4%</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>11.8%</td>
</tr>
</tbody>
</table>
The patients’ most common areas of disease involvement were scalp, beard, and eyebrows, respectively. In addition, 58.8% of the patients had an alopecia attack for the first time, while the other 4 in 10 patients had an alopecia attack for the third time.

Comparison of the gender distribution, mean age, height, weight, BMI, smoking, alcohol consumption, IMA, and albumin levels between the study and control groups are shown in Table 2.

Significant differences were observed between the mean IMA and IMA/albumin ratio (p=0.004 and 0.012, respectively). The study subgroups were comparable for the number of patches, disease duration, and number of disease attacks, as shown in Table 3.

Discussion
The pathogenetic mechanisms of AA have still not been clarified. Impaired immune system activation and genetic predisposition seem to be the main events behind AA. Destruction of hair follicles by immune-mediated cells and inflammatory products results in reversible hair loss in a specific pattern [1]. Excessive oxidative stress is considered to be another triggering event in the development of AA. There are many studies showing the effect of oxidative stress on AA and many other dermatological diseases [10-17]. Degradation products resulting from oxidative stress may damage hair follicles and they may alter the balance between the anagen, telogen and catagen phases. Furthermore, some of these products may be used as biological markers of oxidative stress [18-20].

IMA (ischemic modified albumin) is produced by the modification of albumin due to the reactive oxygen species (ROS). A higher level of IMA was observed in various diseases like ischemic heart disease, pulmonary embolism, cancer, and stroke [21-24]. The role of IMA was also evaluated in dermatological diseases. Elevated levels of IMA were shown in psoriasis, hair diseases, and vitiligo. In recent years, some studies have addressed the risk of thrombosis, acute myocardial infarction, and stroke in AA with various results [25-28]. Shakoei et al. found elevated D-Dimer levels and increased risk of thromboembolism in AA. Kang et al. defined that patients with AA were associated with a higher risk of stroke in the 3-year follow-up period. However, some data do not support the risk of heart attack and stroke in alopecia

### Table 2. Comparison of the gender distribution, mean age, height, weight, BMI, smoking, alcohol consumption, IMA, and albumin levels between the study and control groups.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Patients (n=34)</th>
<th>Controls (n=36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>12</td>
<td>13</td>
<td>0.57</td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>31.56±8.5</td>
<td>31±8.5</td>
<td>0.78</td>
</tr>
<tr>
<td>Height</td>
<td>170.8±9.5</td>
<td>169.7±9.9</td>
<td>0.72</td>
</tr>
<tr>
<td>Weight</td>
<td>72.6±12.8</td>
<td>72.2±10.4</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI</td>
<td>24.79±3.3</td>
<td>25.05±2.8</td>
<td>0.72</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Family history of AA</td>
<td>3</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>IMA</td>
<td>0.71±0.17</td>
<td>0.50±0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.09±0.10</td>
<td>4.08±0.11</td>
<td>0.62</td>
</tr>
<tr>
<td>IMA/Albumin</td>
<td>0.17±0.04</td>
<td>0.12±0.03</td>
<td>0.012</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of IMA, Albumin, and IMA/Albumin according to number of patches, disease duration, and number of disease attacks.

<table>
<thead>
<tr>
<th></th>
<th>Single patch (n=20)</th>
<th>Multiple patch (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of attack</td>
<td>&lt;6 months (n=19)</td>
<td>&gt;6 months (n=15)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>(n=20)</td>
<td>(n=15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMA</td>
<td>0.70±0.20</td>
<td>0.72±0.10</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>0.75±0.21</td>
<td>0.66±0.09</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>0.73±0.21</td>
<td>0.68±0.08</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>0.65</td>
<td>0.40±0.10</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>0.40±0.10</td>
<td>0.40±0.10</td>
<td>0.38</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.17±0.05</td>
<td>0.17±0.02</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>0.18±0.05</td>
<td>0.16±0.02</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>0.18±0.05</td>
<td>0.16±0.02</td>
<td>0.35</td>
</tr>
</tbody>
</table>
areata [27, 28]. On the other hand, recently, in alopecia areata, literature data show a tendency to thrombosis and an increased risk of heart attack and stroke. In addition, studies have found elevated levels of cardiac biomarker troponin I and congestive heart disease biomarker BNP in patients with alopecia areata [29, 30].

There are publications in the literature indicating the association of IMA with the severity and deterioration of AA [9, 31]. These reports focused on the pathophysiological pathways related to increased oxidative stress in patients with AA. As excessive oxidative stress was reported to be an important triggering event in the development of AA, markers associated with oxidative stress might increase with disease severity [32]. Moreover, although the utility of IMA/albumin was investigated in various conditions like chronic liver disease and hemorrhagic shock, to the best of our knowledge, it has not been studied in cases with AA [6, 33]. However, similar to other autoimmune and inflammatory diseases, the etiology of AA is complex, and using a single oxidative biomarker may be insufficient to predict the severe course of the disease [34]. In the present study, no significant differences were observed for IMA and IMA/albumin between the cases with regard to patch characteristics, duration of the disease and number of attacks per year. In our opinion, more studies, including a larger number of cases and many more study parameters, are necessary to reach more reliable results for the role of IMA in the prognosis of AA.

The main strengths of the present study were its prospective design and investigation of IMA/albumin levels in patients with AA. On the other hand, the relatively low number of cases and single-center experience were the main limitations.

In conclusion, although oxidative stress seems to play an important role in the etiology of AA, IMA and IMA/albumin may not be useful in the prediction of disease severity in patients with AA.

References


The Relative Frequency of Small Vessel Cerebrovascular Disease and Brain Atrophy in MRI of Patients with Psoriasis

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Key words: psoriasis, SVCD, MTA, GCA, Fazekas

Citation: Dadkhahfar S, Gheisari M, Mahboubi-Fooladi Z, Shahidi Dadras M. The relative frequency of small vessel cerebrovascular disease and brain atrophy in MRI of patients with psoriasis. Dermatol Pract Concept. 2023;13(1):e2023043. DOI: https://doi.org/10.5826/dpc.1301a43

Accepted: May 19, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Psoriasis is a systemic autoimmune disease that is associated with numerous comorbidities.

Objective: This study aimed to compare the prevalence of small vessel cerebrovascular disease (SVCD) and atrophic brain changes in MRI of patients with psoriasis and normal subjects.

Methods: This case-control study was performed on 27 patients with psoriasis and 27 normal individuals who were referred to Shohada-e-Tajrish Hospital, Tehran, Iran during 2019 and 2020. Basic demographic and clinical information of participants were recorded. Brain MRI was performed for all individuals to examine the medial temporal atrophy (MTA) score, global cortical atrophy (GCA) score, and Fazekas scale. Finally, the relative frequencies of each parameter between the two groups were compared.

Results: There was no significant difference in the frequency of the Fazekas scale, GCA, and MTA scores between the two groups. However, a mild trend was found for a higher frequency of Fazekas scale, GCA, and MTA scores in controls in comparison with the case group. While there was no significant relationship between the Fazekas scale and disease duration (p=0.16), a significant and positive correlation was found between disease duration and GCA and MTA scores (p<0.001). There was no significant relationship between Fazekas, GCA and MTA status and other parameters.

Conclusions: The increase in disease duration was significantly associated with an increase in the incidence of cerebral atrophy, which may suggest the need for screening in terms of CNS involvement in psoriasis patients.
Introduction
Psoriasis is a polygenic immune-inflammatory skin disease [1]. A variety of environmental factors may elicit disease in predisposed individuals. It affects 0.6-5% of the general population in different communities [2]. Psoriasis affects about 8 million adults in the United States, and its overall prevalence in developed countries is about 2% to 3% [3]. The incidence of psoriasis in Iran has been reported between 1.3% and 2.5% (4, 5). About 75% of psoriasis patients have at least one comorbidity such as dyslipidemia, hypertension, diabetes, cardiovascular disease, uveitis, inflammatory bowel disease, osteoporosis and bone involvement, and obstructive pulmonary disease [6].

Some studies have described various neurological and psychiatric involvement such as seizure, stroke, Guillain-Barré syndrome, migraine, and myasthenia gravis in patients with psoriasis. Additionally, there seems to be a higher incidence of cardiovascular and cerebrovascular disease in patients with psoriasis even after eliminating confounding risk factors of vascular disease such as stroke[7].

Small vessel cerebrovascular disease (SVCD) is caused by damage to cerebral microcirculation and often affects the white matter of the brain [8]. About 45% of dementia is caused by SVCD and it accounts for approximately 20% of all strokes worldwide [9, 10]. Clinically, these lesions can range from silent disease to evidence of lacunar infarction, vascular dementia, and other distinct neurological symptoms [11]. Radiological findings include subcortical infarcts, and in advanced stages can be characterized as white matter hyperintensities (WMH), enlargement of the perivascular spaces, lacunae, cerebral microbleeds and atrophy [8, 12]. Depression, cognitive impairment and gait problems, stroke, dementia, and mood disturbance are also commonly found in patients who suffer from SVCD[8]. To the best of our knowledge, no study has examined the extent and the incidence of CSVD in conventional brain MRI of patients with psoriasis. Therefore, we designed and conducted a study to compare the prevalence of SVCD and atrophic changes in conventional MRI of patients with psoriasis in comparison with the control group using medial temporal atrophy (MTA) score, global cortical atrophy (GCA) score and Fazekas scale.

Materials and Methods
This case-control study was conducted on 27 patients with psoriasis and 27 healthy individuals aged 18-60 years old who had been referred to the dermatology department of Shohadaye Tajrish Hospital (Tehran, Iran) between 2019 and 2020. Healthy controls were age and sex-matched individuals who were referred to the dermatology clinic for cosmetic concerns. They also had no considerable history of dermatological disease or previous medical diseases. The control subjects were matched to patients by age and sex. Both groups did not declare past medical history of neurological disease. This case-control study was approved by the institutional review board and ethical committee of Shahid Beheshti University of Medical Sciences. Written informed consent forms were signed by all individuals, including case and control participants. Demographic data of all patients, including gender and age, as well as their medical history, habitual history (including smoking habit), disease duration, nail involvement, and other comorbidities were recorded.

Brain MRI was performed for all patients and controls with the following setting: TR = 9.8 ms; TE = 4.6 ms; flip angle = 8; section thickness = 1.2 mm; number of sections = 120; no section gap; whole-brain coverage; FOV = 224 mm; matrix = 192; reconstruction matrix = 256. Finally, the MTA score, GCA score and Fazekas scale were calculated by an assistant professor of diagnostic radiology with 4 years of experience, to estimate the frequency of brain atrophy and small vessel cerebrovascular disease in each group. The radiologist was blind to whether the images belonged to the case or control group. MTA is a score from 0 to 4 for the assessment of cognitive impairment. The GCA scale is a qualitative rating system from 0 to 3 established to measure cerebral atrophy. The Fazekas scale is used to quantify high signal lesions on T2-weighted imaging in deep white matter and periventricular regions that are usually attributed to chronic small vessel disease (Figure 1) [13].

Statistical Analysis
The results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher’s exact test. Quantitative variables were also compared with t-test or Mann U test. In this study, p<0.05 was considered statistically significant. The SPSS software (IBM, version 19) was applied for the analysis of data.

Results
A total number of 27 consecutive patients with psoriasis and a mean age of 48.14 ± 5.41 years old were entered into the study. The majority of cases (17 out of 27 (63%)) were males. The basic demographic and disease characteristics of all patients are summarized in Table 1. Most patients (74.1%) had nail involvement. Approximately 33% of patients exhibited arthritis and exacerbation. The mean disease duration and PASI score were 10.59 years and 13.74 respectively.

Comparison of the Fazekas scale, GCA and MTA scores between study participants are shown in Table 2. There was
no significant difference in the frequency of the Fazekas scale, GCA and MTA scores between the two groups. However, a mild trend was found for a higher frequency of Fazekas, GCA and MTA with normal status in controls than case group.

The relationships between the Fazekas scale, GCA and MTA scores with other parameters are shown in Table 3. While there was no significant relationship between the Fazekas scale and disease duration (p=0.16), a significant and positive correlation was found between disease duration with GCA and MTA scores (p<0.001). There was no

Table 1: The basic demographic and clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>48.14 ± 5.41</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>No (%)</td>
<td>23 (85.2%)</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>23 (85.2%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Hyper TG (%)</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>Nail involvement</td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>20 (74.1%)</td>
</tr>
<tr>
<td>No (%)</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>9 (33.3%)</td>
</tr>
<tr>
<td>No (%)</td>
<td>18 (66.7%)</td>
</tr>
<tr>
<td>Exacerbation</td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>No (%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>Disease duration (year)</td>
<td>10.59 ± 7.91</td>
</tr>
<tr>
<td>PASI score</td>
<td>13.74 ± 4.42</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
</tr>
<tr>
<td>Methotrexate (month)</td>
<td>27.7 ± 17.65</td>
</tr>
<tr>
<td>Phototherapy (session)</td>
<td>15.23 ± 8.3</td>
</tr>
<tr>
<td>Cyclosporin (month)</td>
<td>14.48 ± 6.5</td>
</tr>
<tr>
<td>Acitretin (month)</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>Sinora (month)</td>
<td>15.7 ± 3.4</td>
</tr>
</tbody>
</table>

Table 2: Comparison of the Fazekas, GCA and MTA between patients and control.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Case</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fazekas scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (55.5%)</td>
<td>14 (51.8%)</td>
<td>0.13</td>
</tr>
<tr>
<td>1</td>
<td>7 (25.9%)</td>
<td>9 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (18.5%)</td>
<td>5 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>GCA scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (88.9%)</td>
<td>20 (74.1%)</td>
<td>0.75</td>
</tr>
<tr>
<td>1</td>
<td>3 (11.1%)</td>
<td>4 (14.8%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 (0.0%)</td>
<td>2 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0%)</td>
<td>1 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>MTA scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.5 (92.6%)</td>
<td>25 (92.6%)</td>
<td>0.87</td>
</tr>
<tr>
<td>1</td>
<td>2 (7.4%)</td>
<td>2 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>
significant relationship between the Fazekas scale, GCA and MTA scores with other parameters such as age, gender, smoking, nail involvement, PASI score, and GCA.

### Discussion

In this study, the relative frequency of brain atrophy and small vessel cerebrovascular disease in brain MRI of patients with psoriasis and normal subjects was compared to age and sex-matched normal individuals. Our results showed that there was no significant difference in chronic small vessel disease measured by Fazekas score. Additionally, the indices of GCA (referring to brain atrophy) and MTA (referring to cognitive impairment) were not significantly different among the case and control groups.

According to our results, age, sex, smoking, disease severity (measured by PASI score) and nail involvement did not have an impact on GCA, MTA scales and Fazekas score.

Interestingly, brain atrophy and cognitive impairment measured by GCA and MTA scales respectively were found to significantly correlate with the disease duration in psoriasis patients. Longer duration of the disease was significantly associated with an increase in cerebral atrophy. This finding can be associated with the fact that chronic plaque psoriasis is an immune-mediated inflammatory skin disease that is strongly associated with the clinical features of metabolic syndrome, and metabolic syndrome can cause alteration in the brain [2, 3]. To the best of our knowledge, the current investigation was the first to reveal an association between psoriasis and increased risk of cerebral atrophy.

Several studies have reported the association between psoriasis and other brain disorders, including cognitive disorders. For example, Gisondi et al.[2], examined the association between psoriasis and cognitive impairment in a case-control design revealing that psoriasis significantly associates with impaired cognitive function.

Similarly, Brown et al. [13], reported that psoriasis may be associated with increased cognitive impairment in these patients. In another study, Innamorati et al., [14] evaluated the association between psoriasis and cognitive impairment in 50 patients with psoriasis and 50 normal individuals. They found that patients with psoriasis had more prominent cognitive impairment, anxiety, depression as well as poorer quality of life.

Recently, Najafi et al., [15] examined the anatomical and functional status of the brain in 14 patients with psoriasis and 15 healthy individuals. They also found that chronic psoriasis could alter brain anatomy. The results of this study are closely consistent with the findings of our research emphasizing that psoriasis could affect brain structures. As in our study, they showed an increased risk of cerebral atrophy in patients with long-term psoriasis. Highlighting the significance of CNS investigation in patients with relevant history and symptoms.

Conversely, in a recent population-based study, Elena Pezzolo et al.[4] found that cognitive test scores and volumetric, microstructural, focal measures on brain MRI did not differ between psoriasis and non-psoriasis participants. They concluded that in this population-based study, psoriasis was not associated with preclinical markers or higher dementia risk. This study differs from our study in terms of the method of white matter evaluation since we subjectively illustrated the white matter changes by Fazekas score.

### Limitations

One of the limitations of this study was the small sample size, which probably affected the comparative results between the control and patient groups to achieve significant differences. Therefore, another study with larger sample size, as well as a long-term cohort can be performed to investigate the association of psoriasis with these parameters.

### Conclusions

Results from the current case-control study support that psoriasis patients are at risk of developing brain atrophy evaluated by Fazekas score. Our study showed that the disease duration in psoriasis patients exhibited a significant relationship with cerebral atrophy. An increase in the disease duration was significantly associated with an increase in the incidence of cerebral atrophy, which can confirm the importance of follow-up for these patients.

<table>
<thead>
<tr>
<th>Fazekas</th>
<th>GCA</th>
<th>MTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.37</td>
<td>0.29</td>
</tr>
<tr>
<td>Gender</td>
<td>0.64</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.72</td>
<td>0.28</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td>0.28</td>
<td>0.3</td>
</tr>
<tr>
<td>Nail involvement</td>
<td>0.42</td>
<td>0.23</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.52</td>
<td>0.67</td>
</tr>
<tr>
<td>Exacerbation</td>
<td>0.35</td>
<td>0.29</td>
</tr>
<tr>
<td>PASI score</td>
<td>0.54</td>
<td>0.46</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
This study provides new insight into comorbidities associated with psoriasis and the necessity of screening psoriasis patients for neurological manifestations.

References

International Dermoscopy Society (IDS) Criteria for Skin Tumors: Validation for Skin of Color Through a Delphi Expert Consensus by the “Imaging in Skin of Color” IDS Task Force

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Key words: dermoscopy, neoplasias, neoplastic dermatoses, skin of color, tumors


Accepted: November 17, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: A structured set of eight basic dermoscopic parameters (lines, clods, dots, circles, pseudopods, structureless, else, and vessels) including a total of 77 variables with corresponding descriptive and metaphoric vocabulary has been released for evaluation of skin tumors by the International
Dermoscopy Society (IDS).
Objectives: To validate the aforementioned criteria for the use in darker phototypes (phototypes
IV-VI) via an expert consensus.
Methods: The two-round “Delphi method” was adopted, with an iterative process including two
rounds of email questionnaires. Potential panelists were asked to take part in the procedure via email
on the basis of their expertise in the dermoscopy of skin tumors in dark phototypes.
Results: A total of 17 participants were involved. All the original variables of the eight basic p
­ arameters
reached agreement during the first round, except for “pink small clods” (“milky red globules”) and
“structureless pink zone” (“milky red areas”). Moreover, during the first round, panelists proposed a
change of three existing items and the introduction of four new items, i.e., “black, small clods” (“black
globules”), “follicular plugs”, “erosions/ulcerations”, and “white color around vessels” (“perivascular
white halo”). All such proposals achieved agreement, thus being included in the final list, for a total
of 79 items. There was consistency between the descriptive and metaphoric approaches in terms of
scoring.
Conclusions: Albeit most of the original items were considered applicable even for skin of color, there
are some points of differences that physicians need to know. No significant preference was found
­between descriptive and metaphoric terminology among panelists.

Introduction

of darker phototypes (e.g., lability of pigment and greater

Dermoscopy has nowadays become an invaluable tool

reasons, the IDS supported a validation process of its con-

for the dermatologist’s daily practice as it allows to high-

sensus document on non-neoplastic dermatoses for use in

light relevant findings corresponding to key histological

dark skin, yet such a procedure has not been performed

changes that are not visible to the naked eye, thus increas-

with regard to neoplastic disorders [8].

tendency to follicular or sclerotic reactions) [6,7]. For these

ing diagnostic accuracy in the field of both neoplastic and

This document was promoted by the “Imaging in Skin

non-neoplastic skin conditions [1,2]. Importantly, to make

of Color” IDS Task Force with the aim of validating the

dermoscopic examination as reproducible as possible it

dermoscopic criteria/terminology provided by the IDS for

is of utmost importance to follow a systematic analytical

skin tumors for the use in skin of color by a consensus

approach, with a standardized set of parameters to evalu-

process involving a panel of experts routinely dealing with

ate and a uniform terminology to use [3-5]. However, over

dark-skinned patients (phototypes IV, V, and VI).

time, many authors employed an arbitrary approach with
the use of different terms, even to refer to the same dermoscopic finding, with a consequent heterogeneous semeiol-

Materials and Methods

ogy generating confusion among users [4]. In order to face

The consensus was performed according to the two-round

such an issue, the International Dermoscopy Society (IDS)

“Delphi method”, with an iterative process including two

has released two consensus documents encompassing ba-

rounds of email questionnaires starting from a list of pre-

sic dermoscopic variables to assess with the corresponding

selected items (i.e., dermoscopic criteria provided by the

vocabulary to adopt, one for skin neoplasms and one for

IDS) [5]. Notably, differently from the “modified Delphi

non-neoplastic dermatoses (inflammatory, infectious, and

method”, the Delphi process makes it possible to gain expert

infiltrative diseases) [4,5]. Notably, these guidelines were

consensus on variable issues by using at least two rounds

issued considering the literature evidence on light photo-

of questionnaires and involving at least 5-10 participants,

types, with consequent possible limitations if used in dark

without the need for an in-person discussion [9-11]. So,

skin [4,5]. Indeed, it has been shown that dermoscopic

similarly to the validation process for skin of color carried

patterns of skin disorders may remarkably vary (espe-

out for non-neoplastic dermatoses [8], we chose to avoid a

cially for phototypes V/VI) because of the different color

face-to-face meeting in order to reduce decisional biases be-

backgrounds as well as specific reaction patterns typical

cause of group interaction [9-11].

2

Original Article | Dermatol Pract Concept. 2023;13(1):e2023067


Panel Selection

Panel selection was performed by sending an e-mail invitation from the coordinators of the process (E.E. and B.S.A.) to experts in the field of dermoscopy in skin of color (phototypes IV, V, and VI) across the world. In detail, all the members of the “Imaging in Skin of Color” IDS Task Force were invited to join the panel, along with researchers who had published at least five peer-reviewed articles or book chapters on such a topic as either the first or last author. In total, 22 international experts were invited as panel members; participants’ assessments were blinded and anonymity was maintained during the entire process of consensus.

Round 1

The dermoscopic criteria provided by the IDS [5] were tabulated (Table 1) and shared with all the panelists via emails, including eight basic dermoscopic parameters with a total of 77 items. As per the original consensus, descriptive terminology and corresponding metaphoric vocabulary for each dermoscopic parameter were included in the validation process. Instructions and aims of the consensus process were also circulated.

Panelists were asked to judge on a 5-point scale the level of agreement on the relevance of each variable (descriptive and metaphorical) for the use in dark-skinned patients (1, no agreement; 2, low agreement; 3, moderate agreement; 4, agreement; and 5, strong agreement). In case of disagreement/poor agreement (score 1-3) on any of the items, participants were invited to justify their choice and provide (optional) suggestions to improve them. Experts were also given the chance to propose additional variables not included in the original list. Each item was considered appropriate for the use in skin of color in case of achievement of a score of 4 or 5 out of 5 by more than 80% of the experts. The agreement threshold of 80% was selected based on the literature guidance on Delphi consensus [10]. Parameters which had not attained 80% agreement would be modified in accordance with suggestions (if any) given by the participants and redistributed, along with new possible proposed items, to the panel of experts for round 2.

Round 2

In round 2, panelists were asked to assess the modified and new parameters (if any) resulting from round 1, following the same methodology as the previous round. At the end of round 2, a comparison between the rating of descriptive and metaphorical terminology for each of the eight basic dermoscopic parameters was carried out. Data were expressed as means ± SD and analysis was performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) by the unpaired, two-tailed student’s t-test, with p-value of <0.05 deemed statistically significant.

Results

A total of 17 participants were involved in both rounds of the consensus. With regard to descriptive terminology, all the items received agreement in round 1 except for “pink small clods” and “structureless pink zone”, which reached a mean score of 3.94 and 3.95, respectively. Similarly, corresponding metaphoric terms for such variables (i.e., “milky red globules” and “milky red areas”) did not achieve agreement too, with a mean score of 3.98 and 3.86, respectively. Four new items were proposed during the first round, i.e., (I) “black, small clods” (black globules) for parameter 2 (“CLODS”); (II) follicular plugs and (III) erosions/ulcercations for parameter 7 (“ELSE”); and (IV) white color around vessels (perivascular white halo) for parameter 8 (“VESSELS”). Moreover, the group of experts suggested changing three items when it comes to descriptive terminology, including (I) “clods, brown or blue, concentric (clod within a clod)” to “clods, brown, blue or black, concentric (clod within a clod)”; (II) “dots, gray” to “dots, gray, blue or black”; and (III) “dots, gray and circles, gray” to “dots, gray, blue or black and circles, gray, blue or black”.

All such proposals were rated during the second round and achieved agreement, thus being included in the final list. Therefore, at the end of the validation process, a total of 79 items were identified (72 out of the 77 proposed by the IDS plus seven added in the course of the consensus procedure). Table 1 displays details on agreement rates and mean scores for rounds 1 and 2. Figures 1-4 depict schematic illustrations of the new/changed items and examples of skin tumors typified by such structures.

Moving to the comparative analysis between descriptive and metaphorical terms of the eight basic parameters, although for the majority of them the mean score was higher for the descriptive counterpart, no statistically significant differences were observed (p-values >0.05).

Discussion

This expert consensus underlines that the whole set of dermoscopic criteria proposed by the IDS for the evaluation of skin tumors may also be used when assessing dark phototypes, apart from “clods, pink and small” and “structureless pink zone, pink” (and corresponding metaphoric terms, i.e., “milky red globules” and “milky-red areas”) as “pink”/“milky-red” hue is more difficult to detect in skin of color because of the pigmented background [6, 12].

In general, most of the variables included from the original IDS list (considering both descriptive and metaphorical
Table 1. Results of the validation process for the use of the IDS dermoscopic criteria (including both descriptive and metaphoric terminology) for neoplastic dermatoses in skin of color with corresponding agreement rates (percentage of experts giving a score of 4 or 5) and mean scores for each round

<table>
<thead>
<tr>
<th>Dermoscopic parameter (Descriptive terminology)</th>
<th>I Round*</th>
<th>II Round*</th>
<th>Dermoscopic parameter (Metaphoric terminology)</th>
<th>I Round*</th>
<th>II Round*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lines, reticular</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Pigment network</td>
<td>100 (4.91)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, reticular and thick</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Broadened network</td>
<td>100 (4.91)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, reticular and thin</td>
<td>100 (4.58)</td>
<td>-</td>
<td>Delicate network</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, reticular and thick or reticular lines that vary in color</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Atypical pigment network</td>
<td>100 (4.91)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, reticular, white</td>
<td>85 (4.25)</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lines, reticular, hypopigmented, around brown clods</td>
<td>92 (4.41)</td>
<td>92 (4.58)</td>
<td>Negative pigment network</td>
<td>100 (4.33)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, white, perpendicularly***</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Shiny white streaks***</td>
<td>84.6 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, branched</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Branched streaks</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, radial (always at periphery)</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Streaks</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, radial and segmental</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Radial streaming</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, radial, connected to a common base</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Leaflike areas</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, radial, converging to a central dot or clod</td>
<td>100 (4.91)</td>
<td>-</td>
<td>Spoke wheel area</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, curved and thick</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Cerebriform pattern</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, brown, curved, parallel, thin</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Fingerprinting</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, curved and thick, in combination with clods</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Crypts</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, parallel, short, crossing ridges (volar skin)</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Fibrillar pattern</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, parallel, thick, on the ridges (volar skin)</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Parallel ridge pattern</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, parallel, thin, in the furrows and crossing the ridges (volar skin)</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Lattice-like pattern</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, parallel, thin, in the furrows (volar skin)</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Parallel furrows pattern</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, angulated or polygonal (facial skin)</td>
<td>92 (4.58)</td>
<td>-</td>
<td>Rhomboids/zig-zag pattern</td>
<td>92 (4.50)</td>
<td>-</td>
</tr>
<tr>
<td>Lines, angulated or polygonal (non-facial skin)</td>
<td>92 (4.50)</td>
<td>-</td>
<td>Angulated lines/polygons</td>
<td>92 (4.52)</td>
<td>-</td>
</tr>
<tr>
<td>Clods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clods, small, round or oval</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Globules</td>
<td>100 (4.50)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, brown, circumferential</td>
<td>92 (4.58)</td>
<td>-</td>
<td>Rim of brown globules</td>
<td>92 (4.51)</td>
<td>-</td>
</tr>
<tr>
<td>Dermoscopic parameter (Descriptive terminology)</td>
<td>I Round*</td>
<td>II Round*</td>
<td>Dermoscopic parameter (Metaphoric terminology)</td>
<td>I Round*</td>
<td>II Round*</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Clods, brown, yellow, or orange (rarely black)</td>
<td>92 (4.52)</td>
<td>-</td>
<td>Comedo-like openings</td>
<td>92 (4.41)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, brown or blue, concentric (clod within a clod)</td>
<td>85 (4.16)</td>
<td>-</td>
<td>Concentric globules</td>
<td>92 (4.42)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, brown or blue or black, concentric (clod within a clod)**</td>
<td>-</td>
<td>100 (4.53)</td>
<td>Concentric globules</td>
<td>100 (4.42)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, brown or skin colored, large and polygonal</td>
<td>100 (4.58)</td>
<td>-</td>
<td>Cobblestone pattern</td>
<td>100 (4.50)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, blue, large, clustered</td>
<td>100 (4.52)</td>
<td>-</td>
<td>Blue-gray ovoid nests</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, blue, small</td>
<td>100 (4.41)</td>
<td>-</td>
<td>Blue globules</td>
<td>100 (4.41)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, black, small</td>
<td>-</td>
<td>100 (4.53)</td>
<td>Black globules</td>
<td>-</td>
<td>100 (4.53)</td>
</tr>
<tr>
<td>Clod within a clod (concentric clods)</td>
<td>85 (4.25)</td>
<td>-</td>
<td>Variant of spoke wheel area</td>
<td>85 (4.30)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, white, shiny***</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Shiny white blotches and strands***</td>
<td>100 (4.56)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, pink and small</td>
<td>72 (3.94)</td>
<td>-</td>
<td>Milky-red globules</td>
<td>72 (3.98)</td>
<td>-</td>
</tr>
<tr>
<td>Clods, red or purple</td>
<td>92 (4.41)</td>
<td>-</td>
<td>Red lacunae</td>
<td>92 (4.23)</td>
<td>-</td>
</tr>
<tr>
<td>3 Dots***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dots, any color</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Granularity or granules</td>
<td>92 (4.54)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, gray</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Peppering</td>
<td>92 (4.52)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, gray, blue or black**</td>
<td>-</td>
<td>100 (5.0)</td>
<td>Peppering</td>
<td>100 (4.52)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, gray and circles, gray</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Annular-granular pattern</td>
<td>100 (4.58)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, gray, blue and black and circles, gray, blue or black**</td>
<td>-</td>
<td>100 (4.53)</td>
<td>Annular-granular pattern</td>
<td>100 (4.58)</td>
<td>-</td>
</tr>
<tr>
<td>Dots or clods, white, clustered or disseminated</td>
<td>92 (4.58)</td>
<td>-</td>
<td>Milia-like cyst, cloudy or starry</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, white, four arranged in a square***</td>
<td>100 (4.51)</td>
<td>-</td>
<td>Rosettes***</td>
<td>92 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, peripheral, arranged in lines</td>
<td>100 (4.53)</td>
<td>-</td>
<td>Linear dots</td>
<td>85 (4.52)</td>
<td>-</td>
</tr>
<tr>
<td>Dots, brown, central (in the center of hypopigmented spaces between reticular lines)</td>
<td>92 (4.48)</td>
<td>-</td>
<td>Targetoid dots</td>
<td>92 (4.32)</td>
<td>-</td>
</tr>
<tr>
<td>4 Circles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circles, white</td>
<td>92 (4.58)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Circles, concentric</td>
<td>92 (4.16)</td>
<td>-</td>
<td>Circle within a circle</td>
<td>92 (4.16)</td>
<td>-</td>
</tr>
<tr>
<td>Circles, incomplete</td>
<td>92 (4.33)</td>
<td>-</td>
<td>Asymmetric pigmented follicular openings</td>
<td>100 (4.12)</td>
<td>-</td>
</tr>
<tr>
<td>5 Pseudopods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudopods, circumferential or lines, radial, circumferential</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Starburst pattern</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1 continues
Table 1. Results of the validation process for the use of the IDS dermoscopic criteria (including both descriptive and metaphorical terminology) for neoplastic dermatoses in skin of color with corresponding agreement rates (percentage of experts giving a score of 4 or 5) and mean scores for each round (continued)

<table>
<thead>
<tr>
<th>Dermoscopic parameter (Descriptive terminology)</th>
<th>I Round*</th>
<th>II Round*</th>
<th>Dermoscopic parameter (Metaphoric terminology)</th>
<th>I Round*</th>
<th>II Round*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Structureless</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structureless zone, brown or black</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Blotch</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless zone, blue</td>
<td>100 (4.58)</td>
<td>-</td>
<td>Blue-whitish veil</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless zone, pink</td>
<td>75 (3.95)</td>
<td>-</td>
<td>Milky-red areas</td>
<td>72 (3.86)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless zone, white</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Scar-like depigmentation</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless zone, white, central</td>
<td>100 (4.83)</td>
<td>-</td>
<td>Central white patch</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless zone, polychromatic</td>
<td>85 (4.33)</td>
<td>-</td>
<td>Rainbow pattern</td>
<td>92 (4.41)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless, red, interrupted by follicular openings</td>
<td>82 (4.16)</td>
<td>-</td>
<td>Strawberry pattern</td>
<td>85 (4.23)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless, brown (tan), eccentric</td>
<td>100 (4.58)</td>
<td>-</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Structureless, any color</td>
<td>100 (4.75)</td>
<td>-</td>
<td>Homogeneous pattern</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Structureless, brown, interrupted by follicular openings (facial skin)</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Pseudonetwork</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>7 Else</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharply demarcated, scalloped border</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Moth-eaten border</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Follicular plugs</td>
<td>-</td>
<td>92 (4.69)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Erosions/Ulcerations</td>
<td>-</td>
<td>100 (4.84)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8 Vessels</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8.1 Morphology</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Dots</td>
<td>100 (4.75)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clods</td>
<td>100 (4.38)</td>
<td>-</td>
<td>Red-purple lacunes</td>
<td>100 (4.46)</td>
<td>-</td>
</tr>
<tr>
<td>Linear</td>
<td>100 (4.75)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coiled</td>
<td>100 (4.58)</td>
<td>-</td>
<td>Glomerular</td>
<td>100 (4.50)</td>
<td>-</td>
</tr>
<tr>
<td>Looped</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Hairpin</td>
<td>100 (4.75)</td>
<td>-</td>
</tr>
<tr>
<td>Serpentine</td>
<td>100 (4.50)</td>
<td>-</td>
<td>Linear irregular</td>
<td>100 (4.58)</td>
<td>-</td>
</tr>
<tr>
<td>Helical</td>
<td>100 (4.50)</td>
<td>-</td>
<td>Corkscrew</td>
<td>100 (4.58)</td>
<td>-</td>
</tr>
<tr>
<td>Curved</td>
<td>100 (4.44)</td>
<td>-</td>
<td>Comma</td>
<td>100 (4.41)</td>
<td>-</td>
</tr>
<tr>
<td>Monomorphous</td>
<td>92 (4.41)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polymorphous</td>
<td>100 (4.75)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dermoscopic parameter (Descriptive terminology)</td>
<td>I Round*</td>
<td>II Round*</td>
<td>Dermoscopic parameter (Metaphoric terminology)</td>
<td>I Round*</td>
<td>II Round*</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
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<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>8.2 Arrangement</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Radial</td>
<td>100 (4.66)</td>
<td>-</td>
<td>Crown vessels</td>
<td>92 (4.50)</td>
<td>-</td>
</tr>
<tr>
<td>Serpiginous</td>
<td>100 (4.66)</td>
<td>-</td>
<td>String of pearls</td>
<td>100 (4.66)</td>
<td>-</td>
</tr>
<tr>
<td>Branched</td>
<td>100 (4.78)</td>
<td>-</td>
<td>Arborizing vessels</td>
<td>100 (4.83)</td>
<td>-</td>
</tr>
<tr>
<td>Clustered</td>
<td>100 (4.83)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Centered dots</td>
<td>100 (4.61)</td>
<td>-</td>
<td>Targetoid vessels</td>
<td>100 (4.63)</td>
<td>-</td>
</tr>
<tr>
<td>8.3 White color around vessels</td>
<td>-</td>
<td>100 (4.53)</td>
<td>Perivascular white halo</td>
<td>-</td>
<td>100 (4.61)</td>
</tr>
</tbody>
</table>

* Agreement rate (mean score) – Agreement rate is measured from 0% to 100%, mean score is measured from 0 to 5;
** This parameter replaces the previous one.
*** Only visible by polarized dermoscopy.
**** Dots and clods can be best differentiated if they appear as a pattern. Multiple dots have the same size and shape (they are all small and round), multiple clods vary in size and shape. In general dots are not larger than the diameter of a terminal hair.
change in the morphology of some structures (e.g., “incomplete” may become “complete” pigmented circles). This is in line with evidence from the literature. For example, blurred vascular structures and “reticular white lines”/“lines, reticular, hypopigmented, around brown clods” (negative pigment network), commonly found respectively in dermal nevi and dermatofibromas in light phototypes, have been reported less frequently in skin of color [13-15].

On the other hand, homogeneous pigmentary findings (excluding concentric and polychromatic items) and white structures were generally rated high (> 4.5). This is easily explained as diagnosis of skin tumors in dark-skinned patients mainly relies on the prevalence and combination of such features [16]. Additionally, some vessel shapes/arrangements also reached a high score, especially dotted/linear morphologies and clustered/branched distribution patterns, likely resulting from the significant prevalence of these findings in Bowen’s disease and basal cell carcinoma also in skin of color [17, 18].

Besides dermoscopic items included in the original list of the IDS, panelists also proposed and agreed on the introduction of four new variables for the assessment of skin tumors in dark phototypes, including “clods, black, small” (black terminology) received a high mean rate (between 4.5 and 5), with only a few of them reaching agreement with a lower score (< 4.5). In detail, the latter group included the following descriptive items: “reticular white lines” and “lines, reticular, hypopigmented, around brown clods” in the “LINES” category; “clods, brown or blue, concentric (clod within a clod)”, “clods, blue, small”, “clod within a clod (concentric clods)” and “clods, red or purple” in the “CLODS” parameter; “dots, brown, central (in the center of hypopigmented spaces between reticular lines)” in the “DOTS” category; “circles, concentric” and “circles, incomplete” when it comes to the “CIRCLES” parameter; “structureless zone, polychromatic” and “structureless, red, interrupted by follicular openings” considering the “STRUCTURELESS” category; and “clods”, “curved” and “monomorphous” morphology in the “VESSELS” parameter. The reasons underlying a lower scoring for such variables mainly include the higher melanin content and the greater tendency to pigmentary incontinence typical of darker phototypes [6] that may result in lower optical contrast (needed to optimally see concentric, polychromatic or pigmented structures) or the partial obscuration of some findings (e.g., red/purple structures, smaller/thinner vessels, or hypopigmented lines) as well as less frequently in skin of color [13-15].

Besides dermoscopic items included in the original list of the IDS, panelists also proposed and agreed on the introduction of four new variables for the assessment of skin tumors in dark phototypes, including “clods, black, small” (black
Figure 2. Examples of skin tumors in dark-skinned patients (phototypes V/VI) typified by the newly-introduced dermoscopic structures: black, small clods (black globules) in a seborrheic keratosis (arrows) (a); follicular plugs in an actinic keratosis (arrows) (b); erosions in a basal cell carcinoma (arrows) (c); and white color around vessels (perivascular white halo) in a squamous cell carcinoma (d).

Figure 3. Schematic representation of modified dermoscopic parameters to use in skin of color: “clods, brown, blue or black, concentric” (clod within a clod) (a); “dots, gray, blue or black” (peppering) (b); and “dots, gray, blue or black and circles, gray, blue or black” (annular-granular pattern) (c).

Figure 4. Examples of skin tumors in dark-skinned patients (phototypes V/VI) typified by the modified dermoscopic parameters: black/brown concentric clods (black clod within a brown clod) in a basal cell carcinoma (arrows) (a); “blue/black dots” (blue/black peppering) in a melanoma (arrows) (b); and “blue/black dots and circles” (blue/black annular-granular pattern) in a lentigo maligna (arrows) (c).
globules), follicular plugs, erosions/ulcerations, and white color around melanin deposits/melanocytes in the epidermis, follicular hyperkeratosis, loss of epidermis/dermis, and acanthosis, respectively. This was due to their significant diagnostic relevance (e.g., follicular plugs are a key clue in actinic keratosis/SCC as they often show a pigmented pattern similar to lentigo maligna/melanoma – see Figures 2b,4c) but also to the higher prevalence of such structures in skin of color (as the result of a greater tendency to darker pigmentation and follicular/ulcerative reactions as well as a greater contrast between the perivascular white halo and surrounding pigmented skin) [6, 19]. Moreover, during the consensus process a change of three existing parameters (i.e., “dots”, “clod within a clod”, and “dots and circles”) was also included, with darker colors (blue/black) being listed as a possible additional hue for the aforementioned structures, still due to the higher tendency to have more prominent pigmentation in dark phototypes [6, 19].

Finally, the comparative analysis between descriptive and metaphoric terminology highlighted no relevant differences in terms of mean score for each of the eight basic parameters, thereby underlying that both of them are useful and might be complementary. In fact, the metaphoric approach is more related to “blink” (quick) diagnoses (e.g., “arborizing” vessels are a quick hint for a basal cell carcinoma), while descriptive assessment is extremely helpful when “blink” fails in describing a lesion and a more analytical process is needed for a correct dermoscopic diagnosis [20, 21]. The lack of a clear predominance between the two approaches is also emphasized by the consistency observed in the present consensus process when considering the rating of each descriptive item and corresponding metaphoric counterpart (<4.0; 4÷4.5; >4.5), with the only exception of “comedo-like openings”.

Indeed, this item was rated lower than the corresponding descriptive terminology, likely because it has a weaker correspondence from a morphological point of view in skin of color as the lower optical contrast typical of dark phototypes often makes epidermal invaginations filled with keratin look like darkly pigmented globules rather than “comedo-like openings” [12].

Conclusions

To conclude, the present validation process provides structured dermoscopic criteria for the assessment of skin tumors in dark phototypes based on parameters proposed by the IDS. Albeit most of the original items were considered applicable even for skin of color, there are some points of differences that physicians need to know. Notably, no significant preference was found between descriptive and metaphoric terminology. The set of criteria validated in this consensus is intended to be the starting point to fill the existing knowledge gap in the field of dermoscopy of skin tumors in skin of color as it might help facilitate the interpretation of reported findings and increase the reproducibility of the studies.

Limitations

The present validation process was based on the Delphi technique, which relies on the opinion of a group of experts, so the results represent the point of view of a limited number of evaluators. Additionally, albeit all the included panelists routinely deal with dark-skinned patients, an interobserver variability does exist in terms of the proportions of each phenotype.

References

7. Errichetti E. Dermoscopy of common papulosquamous dermatoses varies between dark (III and IV) and very dark (V and VI) skin phototypes. Dermatol Ther 2021;34:e14757.


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2 Department of Pediatrics, Castelli Hospital, Verbania, Italy
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Key words: acral dermatitis, COVID-19, COVID-19 toes, pool palms, teledermatology


Accepted: April 24, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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Introduction

Pediatric acral dermatitis represents a diagnostic challenge, as it can have various origins [1], including SARS-CoV-2 infection [2], that can cause acro-ischemic lesions, also called pseudo-chilblain or pernio-like lesions, or “COVID toe”. Due to the mild systemic symptoms, the role of dermatologists is fundamental in the early recognition of the infection and the consequent pandemic containment [2].

We described our real-life experience with teledermatology management of 6 pediatric acral dermatites during the first COVID-19 pandemic. Telemedicine-assisted consultations were conducted to collect anamnestic history and perform skin examination; skin lesions images were independently analyzed by three different dermatologists (GLC, ZE, GF).

Cases Presentation

Case 1: a 6-year-old boy with asymptomatic and symmetrical shiny erythematous-edematous plaques on the toe pads and the fingertips of both hands (Figure 1, A-E). The child had no signs or symptoms and frequented a private pool.

Case 2: a 13-year-old girl with partially exulcerated erythematous-edematous plaques on the toes, fingertips and palms (Figure 1, F-G). Lesions were mildly painful, bilateral...
Figure 1. Clinical aspect of Case 1 (A-E, 6-year-old child) and 2 (F-G, 13-year-old girl): redness and edema symmetrically involving the palmar (A,B,F) and plantar (C,D,E,G) surface of all the distal phalanges of the feet and hands, with the sole exception of the fifth toe; the palms of the hands and feet, in correspondence with the metacarpophalangeal and metatarsophalangeal joints, are also partially affected in case 1. Vesicle-bullous evolution is possible in areas subject to friction on rough pool surfaces (G). Clinical aspect of Case 3 (H-L, 13- and 15-year-old girls) and 4 (M-O, 3-year-old girl): Chilblain-like edematous and erythematous lesions involving the feet, on the dorsal surface (H-I-L), or both on the palmar-plantar and dorsal side (M-N-O). Note the presence of exulcerations on the third and fourth toes (H, L).
and symmetric. The girl attended the family private pool, with a 12 years-old cousin who showed identical lesions.

**Case 3:** two 13- and 15-year-old girls, with chilblain-like burning-aching edematous and erythematosus lesions asymmetrically involving the feet, that completely resolved in about 3 weeks.

**Case 4:** a 3-year-old girl with bilateral and asymmetrical, painful and burning erythematous-violaceous and edematous macules involving the toes and fingers, both on the palmar-plantar and dorsal side (Figure 1, M-O) without systemic symptoms.

SARS-CoV-2 IgG antibodies were positive in both cases 3 and 4.

All 3 dermatologists agreed on the diagnosis of Pool palms (PM), also named “juvenile palmar dermatitis of swimming pools” in cases 1 and 2. Otherwise, in cases 3 and 4 all dermatologists hypothesized COVID-19-related skin lesions, subsequently confirmed by laboratory investigations.

PM is a benign acquired acral dermatosis, typically occurring during childhood (mean age of 6.4 years) [3], probably frequently misdiagnosed with bilateral and symmetrical hand involvement. Table 1 reviews all the 15 PM cases published [3-6]. PM is characterized by erythematous-edematous violaceous asymptomatic lesions with a smooth surface, generally non-infiltrated; in some cases, a painful vesicular-bullous evolution has been described [3-5].

This mechanical dermatosis is caused by repeated rubbing of the palmar and/or plantar skin with the hard and rough walls of the swimming pool. Consequently, the convex areas of the palmar and plantar surface are more affected [3-5]. It is mostly seen in subjects who are learning to swim and so who tend to cling to the pool walls. The dermatosis typically is self-limiting with the interruption of exposure to the pool environment [3-5].

### Table 1. Clinical findings of all reported PM cases, since the first description, dated in 1992*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, Sex</th>
<th>Anatomical Sites involved</th>
<th>Symptoms</th>
<th>Geographical Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgado-Carrasco et al. 2019 PMID: 31921496</td>
<td>5-year-old, F</td>
<td>Palmar surface of the fingers**</td>
<td>Painful lesions</td>
<td>Spain</td>
</tr>
<tr>
<td>Novoa et al. 2016 PMID: 26424817</td>
<td>5-year-old, F</td>
<td>Palmar surface of the fingers**</td>
<td>Asymptomatic lesions</td>
<td>Spain</td>
</tr>
<tr>
<td></td>
<td>4-year-old, F</td>
<td>Plantar surface of the fingers, toe pads and heels**</td>
<td>Asymptomatic lesions</td>
<td>Spain</td>
</tr>
<tr>
<td>Martin JM et al. 2009 PMID: 19709557</td>
<td>6-year-old, F</td>
<td>Palm and palmar surface of the fingers**</td>
<td>Asymptomatic lesions</td>
<td>Spain</td>
</tr>
<tr>
<td>Lopez-Neyra et al. 2009 PMID: 19951653</td>
<td>6-year-old, M</td>
<td>Palmar surface of the fingers**</td>
<td>Asymptomatic lesions</td>
<td>Spain</td>
</tr>
<tr>
<td>Wong et al. 2007 PMID: 17300665</td>
<td>5-year-old, F</td>
<td>Palmar and plantar surface of the fingers**</td>
<td>Not specified</td>
<td>Australia</td>
</tr>
<tr>
<td>Sassolas et al. 1996 PMID: 9033728</td>
<td>10-year-old, M</td>
<td>Palmar surface of the fingers and palms and toe pads**</td>
<td>Painful lesions</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>8-year-old, M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-year-old, M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacour et al. 1995 PMID: 8687057</td>
<td>6-year-old, M</td>
<td>Palmar surface of the fingers and palms**</td>
<td>Not specified</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>4-year-old, F</td>
<td></td>
<td>Asymptomatic lesions</td>
<td></td>
</tr>
<tr>
<td>Blauvelt et al. 1992 PMID: 1619059</td>
<td>12-year-old, F</td>
<td>Palmar surface of the fingers and palms**</td>
<td>Asymptomatic lesions</td>
<td>U.S.A.</td>
</tr>
<tr>
<td></td>
<td>11-year-old, F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 ½-year-old, M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age not specified, M</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: * We performed a systematic review in MEDLINE using the following keywords: “Pool palms”, “juvenile palmar dermatitis of swimming pools” and “dermatite palmaire juvenile des piscines”. Every reference cited in all the articles included has also been verified. Every article that met the search criteria was analyzed, regardless of language (English, Italian, Spanish and French). Gray literature, any document that hasn’t gone through peer review for a publication and conference abstracts were excluded. **Lesions present bilaterally and symmetrically
Conclusions

In the pre-COVID-19 era, allergic contact dermatitis and atopic pulpitis were the main differential diagnoses suggested by several authors [3]. We report the first PM cases reported during the COVID-19 pandemic, proposing a possible potentially underestimated differential diagnosis among childhood acral dermatosis. PM may indeed present clinical features like the acral lesions observed in mild COVID-19 patients; nevertheless, an accurate clinical and anamnestic evaluation can properly orient clinicians (Figure 2).

References


Demographics of Skin Cancer Knowledge Among Middle and High Schoolers in Texas

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Key words: melanoma, education, adolescents, knowledge, demographics

Citation: Zamil DH, Fu S, Majd Z, et al. Demographics of Skin Cancer Knowledge Among Middle and High Schoolers in Texas. Dermatol Pract Concept. 2023;13(1):e2023014. DOI: https://doi.org/10.5826/dpc.1301a14

Accepted: July 4, 2022; Published: January 2023

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Funding: A grant was provided for this study by the Texas Medical Association Alliance.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Adolescents, an age group that can reduce sun exposure early, may benefit from school-based skin cancer education programs. Literature regarding the demographics of melanoma knowledge is sparse.

Objectives: This study sought to evaluate melanoma knowledge among students in Texas viewing John Wayne Cancer Foundation Block the Blaze (JWCFBTB) presentations and identify group differences with regard to sociodemographic factors.

Methods: Before JWCFBTB presentations delivered in Houston and Dallas by health professions students, a pre-presentation melanoma knowledge quiz was distributed. This survey was adapted from a 2000 study evaluating melanoma knowledge in middle and high schoolers in Houston and Dallas. Respondents were also asked to provide their gender, age, grade, race, parent education level, and whether they are first-generation American. ANOVA and Tukey tests were used to evaluate demographic group differences in scores. Logistic regression models determined predictors of answering selected true/false questions correctly.

Results: One-way ANOVA tests showed statistically significant group differences in pre-test scores for all demographic factors evaluated. Females, Whites/Caucasians, students whose parents hold graduate degrees, and older students had higher scores. Black students and non-first-generation Americans were more likely to answer selected commonly missed questions correctly.
Introduction

Accounting for 4% of cancers in adolescents, melanoma of the skin is a common preventable cancer in the United States [1]. Adolescents can reduce sun exposure early, and thus particularly benefit from sun-protective practices [2]. This age group also tends to engage in intentional tanning and may not actively avoid UV exposure [3]. Countries such as Australia have implemented state government and non-governmental organization skin cancer awareness programs, which emphasize childhood prevention, since the 1980s [4]. A 20-year study found that one of these programs, SunSmart, likely contributed to a reduced incidence of melanoma among younger Australians [5]. Additionally, a 2015 review found skin cancer prevention initiatives to be cost-effective and even cost-saving [6]. As such, skin cancer and melanoma awareness initiatives for adolescents in the United States warrant further investigation.

Previous studies have evaluated adolescent knowledge and attitudes towards skin cancer and the efficacy of various school-based interventions. As early as 1992, a Chicago study found that high schoolers spend significant amounts of time in the sun and that a 45-minute intervention increased students’ knowledge of skin cancer [7]. Another study from 2001 found that Texas teenagers under 16 indicated they would limit sun exposure following a melanoma educational quiz exercise [8]. Later research investigated different populations and methods of intervention. Disparities in skin cancer awareness and sun-safe behaviors were found among White Hispanic and White non-Hispanic students in Florida [9]. Among Utah high school students, skin cancer presentations, sunscreen efficacy demonstrations, and distribution of personalized UV damage photos at schools significantly increased sun-protective behaviors in a 1-month follow-up [3]. Finally, medical students have been described as an asset to skin cancer awareness programs for teens; they can offer cost-effective, enthusiastic, and informative melanoma education that can help identify and prevent melanoma [10].

While the literature has extensively investigated attitudes towards and knowledge of skin cancer and melanoma in adults [11–14], few studies have specifically focused on adolescents [15], and even fewer studies have examined school-based interventions addressing knowledge gaps in the US. Moreover, literature regarding adolescents of varying socioeconomic backgrounds or adolescents of racial minorities is sparse [16]. Such knowledge would help identify sociodemographic subgroups that may specifically benefit from more education. This will be essential to targeting skin cancer education programs to the grade levels, age groups, and geographic areas in which they will be most effective.

The John Wayne Cancer Foundation Block the Blaze (JWCFBTB) program, based in California, delivers skin cancer education presentations to youth in 16 states [17]. The Texas branch of the program includes presentations offered at middle and high schools by Baylor College of Medicine medical and physician assistant students. Texas has a high UV index for most of the year [18] and ranks fourth in the nation for estimated new cases of melanoma of the skin in 2020 [1]. Texas is also the second most populous state in the US [19], where people enjoy spending time outside. Thus, early melanoma education in Texas is essential for prevention.

Objectives

As part of JWCFBTB presentations, anonymous surveys are distributed. These include true/false pre-presentation melanoma knowledge quizzes and post-presentation surveys evaluating program efficacy. The objective of this study was to assess the current knowledge of high school students regarding melanoma and skin cancer and examine group sociodemographic group differences in knowledge using pre-presentation survey responses.

Methods

This was a cross-sectional survey study. The pre-presentation true/false melanoma knowledge quizzes and post-presentation surveys utilized in this study were adapted from a previously published study of melanoma knowledge among Texas teenagers [8]. Surveys also collected information on race, parent education level, age, grade, gender, and whether the student is a first-generation American. Middle and high schools in the greater Houston area and Dallas were contacted via email, and 46 virtual JWCFBTB presentations

Conclusions: Results from 2000 and 2020-2021 indicate older students from higher grade levels know more about melanoma, suggesting adolescents may benefit from earlier skin cancer education. Racial minorities and individuals of low socioeconomic status, who suffer from disparities in melanoma treatment and mortality, showed poorer melanoma knowledge. Targeting skin cancer education to disadvantaged schools may help remedy such gaps.
were offered at the 12 schools that responded and scheduled presentations. Survey data was collected between October 14, 2020, and May 25, 2021. Due to the COVID-19 pandemic, JWCFBTB presentations took place virtually, and a link to the survey was sent to all middle and high school students in Texas (Houston and Dallas) watching the presentations. Anonymous responses were collected in a secure spreadsheet. Students were given the option to enter a gift card raffle upon completion of both pre-presentation and post-presentation surveys. To maintain the anonymity of survey responses, students were redirected to a separate link to enter the raffle following survey completion.

The G-power 3.1 statistical software was used for sample size estimation [20]. It was estimated that a total sample of 352 subjects will be needed to provide 80% power to detect significance with a 0.3 effect size for a two-tail analysis t-test at 0.05 α-level. A total of 305 subjects will be needed to provide 80% power to detect significance with a 0.2 effect size for an ANOVA analysis at a 0.05 α-level. A total of 308 students will be needed for a two-tail analysis using logistic regression at a 0.05 α-level, 0.10 β-level (80% power), and for a 1.5 odds ratio. We planned to recruit a minimum of 300 subjects which provides sufficient power for the proposed analysis.

Results

The JWCFBTB presentations were offered to 1279 students in Texas, of which 1154 completed the pre-presentation survey, providing a response rate of approximately 90.3%. The overall average score on the pre-presentation melanoma knowledge test was 64.6%, with a standard deviation of 0.121, a median of 65.6%, and a range of 24.13% to 96.6%. One-way ANOVA tests showed statistically significant group differences in melanoma knowledge pre-test scores for all demographic factors evaluated, including gender (F2,1151 = 21.74; P<.001), race (F2,1148 = 6.10; P<.001), parent educational level (F3,1149 = 3.92; P=.002), age (F4,1149 = 7.70; P<.001), and grade level (F3,1150 = 10.82; P<.001).

For gender (male, female, or other), the Tukey post-hoc test showed higher test scores among females compared to males (η2=0.050; 95% CI, 0.032-0.068; Tukey Honestly Significant Difference (HSD), P<.05). Individuals of multiracial or biracial background scored higher than individuals of Black/African American race (η2=0.059; 95% CI, 0.007-0.112; Tukey HSD, P<.05) and other (Native American/Alaskan Native, ethnicity not listed, prefer not to answer) race (η2=0.064; 95% CI, 0.002-0.126; Tukey HSD, P<.05). Whites/Caucasians also had higher pre-test scores than Hispanics/Latinos (η2=0.031; 95% CI, 0.003-0.059; Tukey HSD, P<.05), Blacks/African Americans (η2=0.052; 95% CI, 0.017-0.087; Tukey HSD, P<.05), and individuals of other race (η2=0.057; 95% CI, 0.009-0.104; Tukey HSD, P<.05). With regards to parent education level, significant differences were only found between two categories: students who answered graduate degree (Master’s, MD, PhD, etc.) had higher scores than those selecting prefer not to answer (η2=0.055; 95% CI, 0.008-0.102; Tukey HSD, P<.05) and 16-17 (η2=0.060; 95% CI, 0.028-0.091; Tukey HSD, P<.05). Students aged 12-13 scored lower than students aged 14-15 (η2=0.043; 95% CI, 0.015-0.071; Tukey HSD, P<.05) and 16-17 (η2=0.060; 95% CI, 0.028-0.091; Tukey HSD, P<.05). Students in grades 9-10 tended to outperform students in grades 5-6 (η2=0.052; 95% CI, 0.018-0.087; Tukey HSD, P<.05) and 7-8 (η2=0.039; 95% CI, 0.014-0.065; Tukey HSD, P<.05). Students in grades 11-12 also scored higher than students in grades 5-6 (η2=0.060; 95% CI, 0.023-0.098; Tukey HSD, P<.05) and 7-8 (η2=0.047; 95% CI, 0.017-0.077; Tukey HSD, P<.05).

Table 1 summarizes the logistic regression results for selecting the correct versus incorrect answer for the True/False statement “Without sun exposure, my body will not produce vitamin D.” Black/African American students were at a greater odd of answering this question correctly than White/Caucasian students (aOR=1.56; 95% CI, 1.03-2.37; P-value=0.007). Additionally, eleventh and twelve graders were at significantly greater odds of answering this question correctly than fifth or sixth graders (aOR=3.41; 95% CI, 1.24-9.37; P-value< 0.04).
and increase early diagnosis [21]. While this highlighted the importance of melanoma education, a PubMed search of “melanoma education” showed that there are only 23 results since 1983, as of August 2021, underscoring the lack of melanoma awareness education programs and research analyzing its efficacy. In this study, we implemented a melanoma education program designed by the John Wayne Cancer Foundation in middle and high schools, with presentations delivered by health professions student volunteers.

This study uses surveys adapted from a school-based melanoma education study that took place in Houston and Dallas in 2000, which found that students aged 16 and older scored 11 percentage points higher, on average, than those between 12-15 years on the melanoma pre-test [8]. The present study found

Table 2 summarizes the logistic regression results for selecting the correct versus incorrect answer for the True/False statement “Melanoma is usually flat, not raised like a mosquito bite or a pimple.” Students who were first-generation Americans were less likely to select the correct answer, as compared to students who were not first-generation Americans (aOR=0.71; 95% CI, 0.55-0.92; P-value= 0.009).

Table 2. Multivariable logistic regression for selecting the correct versus incorrect answer for the True/False statement “Without sun exposure, my body will not produce vitamin D.”

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-13 vs Under 12</td>
<td>0.89 (0.35-2.28)</td>
<td>0.82</td>
</tr>
<tr>
<td>14-15 vs Under 12</td>
<td>0.72 (0.24-2.16)</td>
<td>0.43</td>
</tr>
<tr>
<td>16-17 vs Under 12</td>
<td>0.68 (0.20-2.28)</td>
<td>0.35</td>
</tr>
<tr>
<td>18+ vs Under 12</td>
<td>0.98 (0.23-4.14)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>0.92 (0.70-1.20)</td>
<td>0.45</td>
</tr>
<tr>
<td>Other vs Female</td>
<td>0.49 (0.13-1.87)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander vs White or Caucasian</td>
<td>1.20 (0.85-1.72)</td>
<td>0.15</td>
</tr>
<tr>
<td>Black or African American vs White or Caucasian</td>
<td>1.56 (1.03-2.37)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Hispanic or Latino vs White or Caucasian</td>
<td>1.00 (0.70-1.44)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multiracial or Biracial vs White or Caucasian</td>
<td>0.86 (0.48-1.54)</td>
<td>0.53</td>
</tr>
<tr>
<td>Other vs White or Caucasian</td>
<td>0.62 (0.33-1.16)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>First-generation American</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs No</td>
<td>0.83 (0.64-1.07)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-12 vs 5-6</td>
<td>3.41 (1.24-9.37)</td>
<td>0.04*</td>
</tr>
<tr>
<td>7-8 vs 5-6</td>
<td>2.09 (1.03-4.27)</td>
<td>0.76</td>
</tr>
<tr>
<td>9-10 vs 5-6</td>
<td>2.19 (0.93-5.14)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Highest parent education level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree vs Low education</td>
<td>0.91 (0.56-1.48)</td>
<td>0.56</td>
</tr>
<tr>
<td>Graduate degree (Master’s, MD, PhD, etc.) vs Low education</td>
<td>0.93 (0.59-1.48)</td>
<td>0.66</td>
</tr>
<tr>
<td>Prefer not to answer vs Low education</td>
<td>0.89 (0.46-1.73)</td>
<td>0.68</td>
</tr>
<tr>
<td>High education vs Low education</td>
<td>1.04 (0.62-1.73)</td>
<td>0.72</td>
</tr>
<tr>
<td>Intermediate education vs Low education</td>
<td>1.14 (0.70-1.87)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*aOR = adjusted odds ratio  
CI = confidence interval  
Low education includes the following categories: No schooling, some elementary school, completed elementary school, some middle school, some high school, some trade/vocational school, completed trade/vocational school  
Intermediate education includes the following categories: Completed high school, associate degree  
High education includes the following categories: Some college, some graduate school  
*Indicates statistical significance (significance level P < 0.05)
Although melanoma of the skin is more prevalent among non-Hispanic Whites, survival has been poorer among ethnic minorities since the 1990s, and gaps are worsening over time. Across all minorities, the disparity is growing in patients with localized disease. In patients with distant or regional disease, the disparity is increasing among Hispanic patients [23]. Our study showed White/Caucasian students tended to score higher than minorities such as Hispanics/Latinos and Blacks/African Americans on the melanoma knowledge pre-test. Similar findings were reported from a survey of Boston adults, in which White race positively correlated with melanoma knowledge. Additionally, immigrants and Hispanics could less often define melanoma [24].

These results are corroborated by the present study, in which a similar trend: students aged 12 to 13 tended to score lower than students who were between 14 and 17 years old. Grade level followed the same pattern as high school students (9th-12th grade) scored better than middle school students (5th-8th grade). On one of the most missed true/false questions, “Without sun exposure, my body will not produce vitamin D,” eleventh and twelfth graders were nearly three and a half times more likely than fifth and sixth graders to answer this question correctly. This trend of increasing performance with age, found in Houston and Dallas both in 2000 and 2020-2021, suggests melanoma education programs should target younger students [8]. As sun exposure is cumulative [22], it is essential to expose students to information regarding skin cancer early and to bridge the knowledge gap between younger and older students.

### Table 2. Multivariable logistic regression for selecting the correct versus incorrect answer for the True/False statement “Melanoma is usually flat, not raised like a mosquito bite or a pimple.”

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-13 vs Under 12</td>
<td>2.10 (0.90-4.92)</td>
<td>0.12</td>
</tr>
<tr>
<td>14-15 vs Under 12</td>
<td>1.46 (0.53-4.05)</td>
<td>0.99</td>
</tr>
<tr>
<td>16-17 vs Under 12</td>
<td>1.26 (0.41-3.89)</td>
<td>0.50</td>
</tr>
<tr>
<td>18+ vs Under 12</td>
<td>1.72 (0.43-6.80)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>1.07 (0.82-1.39)</td>
<td>0.62</td>
</tr>
<tr>
<td>Other vs Female</td>
<td>1.56 (0.49-5.00)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Race</strong></td>
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<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander vs White or Caucasian</td>
<td>0.97 (0.69-1.37)</td>
<td>0.89</td>
</tr>
<tr>
<td>Black or African American vs White or Caucasian</td>
<td>0.90 (0.59-1.37)</td>
<td>0.58</td>
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<tr>
<td>Hispanic or Latino vs White or Caucasian</td>
<td>1.08 (0.75-1.54)</td>
<td>0.54</td>
</tr>
<tr>
<td>Multiracial or Biracial vs White or Caucasian</td>
<td>1.04 (0.59-1.81)</td>
<td>0.83</td>
</tr>
<tr>
<td>Other vs White or Caucasian</td>
<td>0.95 (0.54-1.67)</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>First-generation American</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs No</td>
<td>0.71 (0.55-0.92)</td>
<td>0.009*</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
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<tr>
<td>11-12 vs 5-6</td>
<td>1.06 (0.41-2.80)</td>
<td>0.57</td>
</tr>
<tr>
<td>7-8 vs 5-6</td>
<td>0.80 (0.42-1.56)</td>
<td>0.41</td>
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<tr>
<td>9-10 vs 5-6</td>
<td>0.84 (0.38-1.88)</td>
<td>0.58</td>
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<tr>
<td><strong>Highest parent education level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree vs Low education</td>
<td>0.62 (0.38-0.99)</td>
<td>0.17</td>
</tr>
<tr>
<td>Graduate degree (Master’s, MD, PhD, etc.) vs Low education</td>
<td>0.82 (0.52-1.28)</td>
<td>0.38</td>
</tr>
<tr>
<td>Prefer not to answer vs Low education</td>
<td>0.54 (0.28-1.03)</td>
<td>0.16</td>
</tr>
<tr>
<td>High education vs Low education</td>
<td>0.80 (0.48-1.31)</td>
<td>0.61</td>
</tr>
<tr>
<td>Intermediate education vs Low education</td>
<td>0.75 (0.46-1.22)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*aOR = adjusted odds ratio
CI = confidence interval
Low education includes the following categories: No schooling, some elementary school, completed elementary school, some middle school, some high school, some trade/vocational school, completed trade/vocational school
Intermediate education includes the following categories: Completed high school, associate degree
High education includes the following categories: Some college, some graduate school
*Indicates statistical significance (significance level P < 0.05)
first-generation Americans were less likely to answer the true/false statement “Melanoma is usually flat, not raised like a mosquito bite or a pimple” correctly. One unique finding in the present study was that Black/African American students were more likely to answer the true/false statement “Without sun exposure, my body will not produce vitamin D” correctly, as compared to White students.

Research has shown greater melanoma mortality rates among individuals of low socioeconomic status due to a lack of access to care and early detection [25,26]. However, group differences in scores between students stratified by parental education level were not as pronounced as other demographic factors. Nonetheless, remediation of generally poorer melanoma outcomes and general knowledge among disadvantaged populations and minorities may benefit from school-based education programs to increase awareness of melanoma and sun-protective behaviors.

With regards to gender, females outperformed males on the melanoma knowledge pre-test. As women are at a lower odds of developing skin cancer than men in the US, males may especially benefit from skin cancer education in schools [27]. Although this study did not feature a large sample size of gender minorities, literature has shown a disproportionate skin cancer burden among gender and sexual minorities, as well as unique risk factors for skin cancer in these populations [28,29].

Conclusions

Overall, on a melanoma education knowledge test given to middle and high schoolers before a skin cancer awareness presentation, this study found lower scores among racial minorities and students of younger ages and lower grade levels. Students who were Black, older, or who were not first-generation Americans were more likely to select the correct answer on a subset of the most missed questions on the test. Limitations of this study include self-reported data by the students and general cross-sectional design limitations, as well as a sample limited to schools where Baylor College of Medicine students were able to offer presentations. Future directions include analyzing the results of the post-presentation surveys from the same educational program to determine program efficacy.

Acknowledgements

We would like to thank Dr. Anthony Lucci, Lauren Fraga, Mayra De La Cruz, Yasmin Khalife and the John Wayne Cancer Foundation for their guidance and support in conducting this study. We would also like to acknowledge Kristiana Nasto, Amna Bashir, Rujman Khan, Sahifah Ansari, Rachel Stroh, Nicole Walters, Ebubechi Adindu, Ruth Mizu, Milbrey Parke, Louisa Liu, Tiffany Tran, Hangqing Shang, Joanne Jacob, Rohit Gupta, Tejas Joshi, and Xiaoman Yu for their role in data collection. Funding for the inaugural chapter of John Wayne Cancer Foundation’s Block the Blaze program at Baylor College of Medicine was provided by the Texas Medical Association Alliance.

References


Silicone Models for Dermatological Education: Assessment of a New Teaching Tool by Dermatologists

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Key words: dermatological education, teaching tool, silicone models, 3D models, evaluation


Accepted: April 21, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: The coronavirus pandemic forced universities to transfer academic curricula into the digital realm and calls for the introduction of new teaching methods to adequately compensate for the limited in-patient training. Especially in the field of dermatology, the use of 3D models presents an interesting opportunity to maintain the teaching of diagnostically essential sensory and haptic characteristics of primary lesions.

Objectives: We developed a prototype silicone model and presented it to the medical service of the Department of Dermatology of the Ludwig-Maximilians University for evaluation.

Methods: Silicone models demonstrating primary skin lesions were produced by using negative 3D-printed molds and different types of silicone. An online survey obtained evaluations from a group of dermatologists regarding the quality of previously supplied silicone 3D models and their potential use in medical education. Data from 58 dermatologists were collected and analyzed.

Results: The majority of the participants rated the models overall as positive and innovative, providing constructive feedback for additional modifications, and recommended further implementation into the regular curriculum as an additional tool after the end of the pandemic.

Conclusions: Our study underlined the possible advantages of using 3D models as a supplement in educational training even after the end of the SARS-CoV-2 pandemic.
Introduction

At the beginning of 2020, the pandemic outbreak of the coronavirus SARS-CoV-2 necessitated a quick shutdown of most public life in Germany to contain dissemination. Accordingly, universities were confronted with new challenges to continue providing high-quality education.

For most faculties, this entailed a drastic transition into the digital realm. However, a couple of specialist fields depending on physical practices could not properly substitute essential courses. Medical education in particular is heavily reliant on face-to-face contact with patients both to learn clinical pictures as well as to improve important communication skills. Different approaches already aimed to expand learning and teaching strategies beyond traditional methods even before the pandemic urged educators to revise their formerly established curriculum. Case discussions and inverted classroom courses incentivize a more active engagement of students, whereas websites and a range of mobile learning applications, e.g. for dermatological education, encourage auto-didactic learning[1-3]. Furthermore, patient-orientated-communication courses use actors to simulate true-to-life clinical situations. However, these approaches are still not able to substitute the in-patient examination of haptic manifestations of symptoms, the lack of which constitutes a major disadvantage of currently used teaching methods[4, 5]. Therefore, other medical fields have already implemented the use of 3D models in training and education, for example in anatomy, dentistry and surgical preparations[6, 7].

Expanding on this idea, we created colored 3D silicone models with texturized surface areas to emulate common primary skin lesions. Since visual and haptic examination of the skin plays a major role in dermatological differential diagnosis[8], this model should be especially useful in times of restricted patient access and possibly as a general learning tool as well.

In this study, an early version of our 3D-printed model of primary skin lesions was shown to a group of dermatologists to evaluate the quality of the model and state their opinion about the study object, possible benefits for students and acquired knowledge about moulages and their opinion regarding an online survey addressed to dermatologists of the Ludwig-Maximilian-University (LMU) in Munich/Germany to use their knowledge and dermatological expertise in the assessment of silicone models in medical teaching. Questions were answered using a grading from strongly agree, agree, neutral, disagree to strongly disagree. The survey was in German language and carried out completely anonymously (translated version Suppl. File 1).

Participants were asked about their work experience, acquired knowledge about moulages and their opinion about the study object, possible benefits for students and suggestions for improvement.

Methods

Silicone Models

Our study object was a silicone model demonstrating primary skin lesions. The silicone models were produced using negative molds made from polylactide (PLA) using Martz PLA Matt Filament (IGO3D GmbH, Hannover, Germany) on the 3D printer Anycubic i3 Mega S printer (ShenZhen ANYCUBIC Technology Co., Ltd, Shenzhen, Guangdong, China). The layer height was adjusted to 0.1 mm without any support structures or attachment layers. The platform temperature was set at 60° C with an extrusion temperature of 200° C. Subsequently, a cotton swab soaked in tetrahydrofuran (Sigma Aldrich, Steinheim, Germany) was repeatedly used to smooth the molds. TinkerCAD online software (Autodesk, Inc, San Rafael, California, USA) was applied for designing the molds. The slicing software used was Ultimaker Cura (version 4.8, Ultimaker BV, Utrecht, Netherlands).

Next, after degassing for 1 minute using a vacuum pump (diaphragm vacuum pump, Vacubrand GmbH+Co., Wertheim, Germany), we poured silicone rubber (equal amounts of part A and B) according to the lesion properties (Suppl. File 1), polymerized overnight at room temperature and applied normal skin as the last layer on the second day (all materials: KauPo Plankenhorn e.K., Spaichingen, Germany). After another overnight polymerization period, the silicone model was stripped off and stuck onto a postcard sized (approximately 10.5 cm × 14.8 cm) overhead transparency (Figure 1A). Finally, to obtain a matt surface finish our models were powdered with household starch.

Survey

In February 2021, we performed a longitudinal study using an online survey addressed to dermatologists of the Ludwig-Maximilian-University (LMU) in Munich/Germany to use their knowledge and dermatological expertise in the assessment of silicone models in medical teaching. Questions were answered using a grading from strongly agree, agree, neutral, disagree to strongly disagree. The survey was in German language and carried out completely anonymously (translated version Suppl. File 1).

Participants were asked about their work experience, acquired knowledge about moulages and their opinion on incorporating 3D models into dermatological education in general.

Statistics

Statistical calculations were done using SPSS statistics 26.0 (IBM Corp., released 2019, Armonk, NY/USA), visualizations were performed using GraphPad Prism version 9.0.0 (GraphPad Software, La Jolla, CA). Metric variables were indicated as mean values ± standard deviation (SD). P value was calculated by using the Mann-Whitney Test. Significance level was set at P<.05. The data were evaluated descriptively. Ethical approval was obtained from the committee of the LMU (project KB 20/031).

Results

Study Population

Fifty-eight dermatologists participated in the survey. Thirty-eight participants were female (65.5%), and twenty
Figure 1. A: Study object (silicone model): Upper row illustrating patch (Macula), plaque (Plaque) and wheal (Urtica), lower row depicting papule (Papula), nodulus (Nodulus), nudule (Nodus), pustule (Pustula) and vesicle (Vesicula) (left to right, respectively; Latinized German terms in brackets). B: Age and gender distribution of all participants (left panel). Experience with moulages depending on working experience (right panel). C: Exemplary represented assessment (from “strongly agree” to “strongly disagree”) for different evaluation criteria.
participants were male (34.5%). The current mean age was 34.6 years (range 25 – 64 years). Among all participants, thirty-eight (65.5%) were dermatological residents with less than five years of working experience. Nine doctors were attending physicians (15.5%) and worked between five and ten years in the field of dermatology and eleven (mainly advanced attending physicians) (19.0%) worked for more than ten years as dermatologists. Overall, fifty-one doctors (89.5%) stated that they have not worked or taught students by using moulages while six participants (10.5%) have already gained experience by using them. Doctors who already used moulages provided a significantly higher working experience (P=.003) (Figure 1B).

Survey

To review the true-to-life properties of the silicone models, the participants were asked if they would assess the moulage as realistic in terms of sensory and haptic perception. Almost two-thirds (62.5%, 35/56) answered “strongly agree”, a quarter (25%, 14/56) answered “agree” and 12.5% (7/56) answered “neutral or strongly disagree”.

Subsequently, when asked whether the model was representative of the clinical picture regarding haptic properties, 50.9% (28/55) answered “strongly agree” 34.5% (19/55) answered “agree” and 14.6% (8/55) answered “neutral or disagree”. Furthermore, 65.5% (36/55) answered “strongly agree” when asked if the models are of good quality regarding their elaboration, 29.1% (16/55) answered “agree” and 5.4% (3/55) answered “neutral or disagree”.

More than three-quarters (76.4%, 42/55) of the participants strongly agreed that the model was sufficient in size, while 18.2% (10/55) agreed and the rest (5.4%, 3/55) answered “neutral or disagree”. Additionally, when asked if the model was of a handy size, 80% (44/55) answered “strongly agree”, 18.2% (10/55) answered “agree” and only one participant (1.8%, 1/55) answered “neutral”. Subsequent questions regarded the use of models as learning/teaching tools. Therefore, participants were asked if they considered the training with models as innovative regarding the current situation. Over two-thirds (69.1%, 38/55) answered “strongly agree”, 27.3% (15/55) answered “agree” and 3.6% (2/55) answered “disagree or strongly disagree” (Figure 1C).

Additionally, when asked if they would expect the moulages to facilitate the student’s learning approach, 74.5% (41/55) answered “strongly agree”, 20% (11/55) answered “agree” and 5.4% (3/55) answered “neutral or disagree”.

More than two-thirds (67.3%, 37/55) of the dermatologists strongly agreed that they consider the moulages a good supplement to in-patient teachings even after the end of the pandemic. Almost a quarter (23.6%, 13/55) answered “agree” and 9% (5/55) answered “neutral, disagree or strongly disagree”.

However, 61.8% (34/55) of the participants strongly agreed that the models should be expanded to include secondary lesions or dermatological clinical pictures as well. Over a quarter (27.3%, 15/55) answered “agree” and 10.9% (6/55) answered “neutral, disagree or strongly disagree”.

To evaluate possible benefits of the 3D-printed models, the participants were asked if they would deem the silicone moulages advantageous over the more traditional, usually wax-based models, to which almost two-thirds (65.5%, 36/55) strongly agreed, while 25.5% (14/55) answered “agree” and 9.1% (5/55) answered “neutral”.

Finally, the participants were asked to rate the general idea of teaching with silicone moulages on a scale ranging from very good (1) to poor (5), to which 72.7% (40/55) answered “very good”, while 20% (11/55) answered “good” and only 7.3% (4/55) answered “moderate or poor”.

Additionally, the participants had the opportunity to comment on their perceived shortcomings and their general opinion of the silicone moulages in two open-ended questions. Constructive criticism involved suggestions to modify color, haptics and size to improve resemblance to actual clinical cases. However, one comment stated that the models are, although nice to have, rather irrelevant since students have always been able to correctly identify primary lesions without additional teaching methods.

Almost all of the participants gave positive feedback, complimenting the resourcefulness and good realization, as well as describing the model as a great supplement to the traditional teaching methods and long-distance teaching tool, especially in times of limited patient contact due to COVID-19 restrictions.

Discussion

In the medical field, providing the best possible education and preparation of students for clinical practice at any given time is of paramount concern. Usually, this is accomplished by connecting the knowledge obtained by lectures and textbooks with actual clinical pictures via bedside teaching. However, times of limited patient access impose the need for alternative substitutional methods.

Physical 3D models have already found their way into various medical fields to better illustrate spatial visualization of anatomical features and pathologies, rendering them a suitable candidate for a contactless teaching experience[6]. Various studies reported improvements in students’ self-perceived knowledge and confidence following an auto-didactic study session[9]. Furthermore, studies have shown an objective increase in knowledge acquisition[10, 11], even proving to be superior in direct comparison with cadaveric material[12], CT scans or 3D computer simulations[13, 14]. All aforementioned studies additionally received positive feedback from
students, who expressed wishes to incorporate the 3D models into the regular curriculum.

Correspondingly, medical experts also reported their satisfaction with the models and emphasized their usefulness in medical education[15]. These findings concur with our own results, as the idea of 3D models generally yielded a very positive response, and the majority of questioned dermatologists found the silicone models to be innovative and to facilitate learning of primary lesions. Although it was noted that 3D models cannot fully encapsulate the visual and sensory representation of primary lesions and are therefore not able to replace the clinical picture, the models primarily attempt to create a basic understanding in students with little to no clinical dermatological experience. This is especially crucial since dermatological problems are numerous and often occur as comorbidities in a variety of medical domains[16].

Additionally, the restricted ability to replicate the clinical picture in complete detail should not be seen as a limitation, considering the model an auxiliary teaching tool rather than a replacement for in-patient training once the pandemic subsides. For this application, our study yielded almost universal approval among participants.

Improvement suggestions stated in the open-ended questions regarded slight modifications of color, size and haptic characteristics. Since the nature of the silicone models allows for quick and easy incorporation of feedback, our prototype model can be constantly upgraded utilizing these suggestions at a fairly low price point (approximately 50 Eurocent (0.5 €) per model).

Conclusions

In conclusion, experts approved the utilization of silicone 3D-printed models as a highly promising method in dermatological education in times of restricted in-patient contact and further recommended the incorporation of the models as an additional tool into the regular curriculum.

References

Significant Association between Obsessive-Compulsive Disorder and Atopic Dermatitis – a Retrospective Population-Based Case-Control Study

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Key words: atopic dermatitis, obsessive-compulsive disorder, comorbidities


Accepted: June 27, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a global health problem. There are no data on the association of AD with obsessive-compulsive disorder (OCD).

Objectives: This study aimed to map a wide spectrum of different diseases among patients with atopic dermatitis compared to healthy controls in the Region of Jönköping County, Sweden with special focus on OCD.

Methods: We conducted a retrospective case control study from January 1st 2013 until December 31st 2021 using an electronic medical records database covering the entire population of the County of Jönköping. ICD-10 codes were used to identify patients with AD. Individuals without AD served as controls. A total number of 398,874 citizens under the age of 90 was included in this study and among these 2,946 individuals were diagnosed with AD. Regression analysis was performed to describe the risk for comorbidities in patients with AD compared to controls, adjusted for age and gender.

Results: We found an association between obsessive-compulsive disorder (OCD) in patients with AD (adjusted odd ratio 2.0, 95% confidence interval 1.5-2.7, p<0.001). Other results are in the line with other studies.
Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease with a lifetime prevalence of up to 20% [1]. The disease is associated with an impaired skin barrier, elevated levels of total immunoglobulin E (IgE) and immune dysregulation. Genetic predisposition and environmental triggers are likely involved in causing the disease [2]. Treatment strategies usually involve moisturizing regimes, topical anti-inflammatory preparations, phototherapy and, in severe cases systemic therapy [3, 4]. AD usually develops in children as part of the atopic march, thus frequently occurs together with asthma and allergic rhinitis in the same individual [5]. Different subtypes of hand eczema are additional conditions that have well-established associations with AD [6]. Several studies have indicated that the burden of comorbidity reaches well beyond the atopic march and hand dermatitis [7-9]. Previous studies have shown that patients with AD have an increased risk of bacterial, viral and fungal infections [9-12]. Several studies have detected a positive association between AD and allergic and autoimmune diseases. Furthermore, alopecia areata has been shown to increase the risk of AD [8]. Most recently, a large population-based study conducted in Sweden has indicated significant autoimmune comorbidity of adults with AD, pointing to autoimmune dermatological, gastrointestinal and rheumatological diseases [13].

An association between overweight/obesity and AD has been significantly observed in North America and Asia, but not in Europe [14]. Data has shown a greater risk for congestive heart failure and coronary artery disease in adults with AD, while results on increased risk in AD for myocardial infarction and stroke have varied [15].

The association between AD and cancer is the subject of several previous studies but results are ambiguous. [8, 16]. Depression, suicidality and anxiety are more frequently occurring in patients with AD compared to the non-AD population [17, 18]. Several studies show that atopic disease and atopic eczema correlate to an increased risk of developing attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder later in life [19-21]. Data is limited when it comes to the association between AD and obsessive-compulsive disorder (OCD). Two studies examined the association of OCD in mothers of children with AD where results showed that having a child with AD does not influence their mothers in terms of OCD and health-related quality of life [21, 22].

Objectives

Establishing comorbidity seen in AD can help to further understand the complex pathogenesis of AD, contribute to finding improved treatment strategies, and thus improve quality of life in AD patients. Consequently, studies investigating comorbidities related to AD are of great importance in order to screen for and treat them as early as possible. This study aimed to determine the association between AD and selected diagnoses, including OCD, in the population of the Region Jönköping, Sweden.

Methods

In this retrospective population-based case-control study, patients and controls were identified from Cosmic R8; the electronic medical record (EMR) used by the regional healthcare provider. All registered citizens of the Region Jönköping under the age of 90 were included from January 1, 2013, until December 31, 2021, also including those who had never contacted a regional state facility. The case group included all individuals with one of the following ICD-10 diagnoses; L209 Atopic dermatitis, unspecified; L208A Atopic dermatitis in children without food allergy; L208B Atopic dermatitis in children with food allergy; L208G Atopic dermatitis in adults; registered in the Dermatology and Venereology Clinic or in the Pediatric Clinic. The control group included all citizens of the region who had never been diagnosed with one of the mentioned L20- diagnoses in one of the two clinics. For each individual, data was collected about gender and age. In the case group, age was defined as the patients’ age the first time they acquired an AD diagnosis and for controls as their age on December 31, 2021. Ethical approval for this study was obtained by Swedish Ethical Review Authority (Dnr 2022-00212-01).

A literature search was performed in PubMed on articles exploring atopic dermatitis and comorbidities and resulted in an arbitrary selection of 82 comorbidity diagnoses. Each individual, both cases and controls, was matched with each comorbidity in Cosmic R8 and it was registered if they had received one of the diagnoses during the test period. The data

Conclusion: Pointing to previous studies, the cause of AD and OCD share several gene-environmental mechanisms and this association should be further studied on larger populations. The results of the present study underline the need for dermatologists to be aware of OCD and to screen for this condition in AD patients because early diagnosis and treatment may improve outcome.
was coded so that the person performing the analysis was blinded to personal information about the subjects.

Data were processed into a Statistical Package for the Social Sciences (IBM SPSS version 27.0) data sheet for statistical analysis. Continuous data were described as mean±SD. To estimate the risk of comorbidity the odds ratio (OR) presented with a 95% confidence interval (CI) was calculated using a binominal logistic regression and ORs were adjusted for age and sex and presented as such unless stated otherwise.

Results

The study included all 398,874 citizens of Jönköping County under the age of 90 that were registered in Cosmic R8 and were alive on December 31, 2021. Among these, 2,946 (0.7%) were included in the case group and 395,928 (99.3%) in the control group. There were 1,229 males and 1,717 females in the case group and 201,732 males and 194,196 females in the control group. The mean age in the case group was 23.2 years and most patients (34.6%) were seen in the age groups 0-9. The control group had a more homogenous distribution between the age groups and a mean age of 40.5 years. (Table 1)

Our results showed that patients with atopic dermatitis had an increased risk for several comorbidities including OCD (OR = 2.0; 95% CI = 1.5-2.7), anxiety disorders (OR = 1.5; 95% CI = 1.4-1.7), depressive episodes and sleep disorders (OR = 1.4, 95% CI = 1.3-1.6; OR = 1.8, 95% CI = 1.6-2.0) (Table 2). Further, ADHD was significantly increased in AD.

Furthermore, our result indicated a positive association between AD and autoimmune disorders such as vitiligo (OR = 3.5; 95% CI = 2.2-5.4), alopecia areata (OR = 3.9; 95% CI = 2.8-3.5), Crohn’s disease (OR = 3.4; 95% CI = 2.4-4.9) as well as ulcerative colitis (OR = 2.2; 95% CI = 1.5-3.2).

Positive associations were seen among infections: other bacterial intestinal infections (OR = 2.4; 95% CI = 1.7-3.4), erysipelas (OR = 3.4; 95% CI = 2.8-4.2), streptococcus and staphylococcal infection (OR = 5.9; 95% CI = 4.6-7.4), herpes viral infections (OR = 3.3; 95% CI = 2.8-3.9), viral infections (OR = 1.6; 95% CI = 1.5-1.7), dermatophytosis (OR = 2.5; 95% CI = 2.2-2.8), candidiasis (OR = 2.1; 95% CI = 1.8-2.4), Lyme disease (OR = 1.7, 95% CI = 1.4-2.0) and impetigo (OR = 4.9; 95% CI = 4.5-5.4) and streptococcal sepsis were significantly associated with AD (OR = 3.9; 95% CI = 1.3-12.3).

Significantly increased risk of having cardiovascular disorders for patients with AD was found for hypertension (OR = 2.2; 95% CI = 1.9-2.6), dyslipidaemia (OR = 1.8, 95% CI = 1.5-2.2), atherosclerosis (OR = 3.5; 95% CI = 1.9-6.2), cerebral infarction (OR = 3.0; 95% CI = 2.0-4.6), angina pectoris (OR = 1.9; 95% CI = 1.3-2.8) and chronic ischemic heart disease (OR = 2.0; 95% CI = 1.5-2.8). The diagnosis Z72 Problems related to lifestyle was significantly increased in the AD group (OR = 1.5, 95% CI = 1.3-1.8). The diagnoses include the sub-diagnoses Z72.0 Tobacco use,

| Table 1. Table showing patients demographics patients with atopic dermatitis and controls. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age             | Atopic Dermatitis | Controls         |                 |                 |
|                 | M   | F   | M   | F   | M   | F   | M   | F   |                 |
| Mean (aSD)      | 23.2 (20.6) | 19.9 (20.5) | 25.6 (20.3) | 40.5 (23.8) | 39.9 (23.5) | 41.0 (24.1) |
| 0-9             | 989 | 935 | 454 | 45012 | 11.4 | 23106 | 21906 |
| 10-19           | 531 | 217 | 314* | 46627 | 11.8 | 23916 | 22711 |
| 20-29           | 474 | 138 | 336** | 54388 | 13.7 | 28376 | 26012 |
| 30-39           | 319 | 92  | 227# | 55676 | 14.1 | 29045 | 26631 |
| 40-49           | 228 | 98  | 130& | 45980 | 11.6 | 23725 | 22255 |
| 50-59           | 189 | 78  | 111b | 48409 | 12.2 | 24908 | 23501 |
| 60-69           | 123 | 41  | 82  | 41034 | 10.4 | 20813 | 20221 |
| 70-79           | 78  | 27  | 51  | 38717 | 9.8  | 19093 | 19624 |
| 80-89           | 15  | 3   | 12  | 20085 | 5.1  | 8750  | 11335 |

n = number, M = male, F = female
* OR for females to develop eczema is 1.517 (95% CI 1.277-1.801)
** OR for females to develop eczema is 2.635 (95% CI 2.163-3.210)
* OR for females to develop eczema is 2.677 (95% CI 2.102-3.409)
** OR for females to develop eczema is 1.412 (95% CI 1.087-1.834)
* OR for females to develop eczema is 1.506 (95% CI 1.128-2.011)
** OR for females to develop eczema is 2.054 (95% CI 1.413-2.987)
* OR for females to develop eczema is 1.836 (95% CI 1.152-2.925)
<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>ICD-10-code</th>
<th>Atopic dermatitis (n=2946) n (%)</th>
<th>OR (95% CI)</th>
<th>Adjusted OR * (95% CI)</th>
<th>Significance level **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly allergic asthma</td>
<td>J45.0</td>
<td>177 (6.0)</td>
<td>8.6 (7.3-10.1)</td>
<td>6.4 (5.5-7.5)</td>
<td>***</td>
</tr>
<tr>
<td>Vasomotor and allergic rhinitis</td>
<td>J30</td>
<td>897 (30.4)</td>
<td>4.0 (3.7-4.4)</td>
<td>4.2 (3.8-4.5)</td>
<td>***</td>
</tr>
<tr>
<td>Acute atopic conjunctivitis</td>
<td>H10.1</td>
<td>530 (18.0)</td>
<td>6.4 (5.8-7.0)</td>
<td>5.6 (5.1-6.2)</td>
<td>***</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>L80</td>
<td>21 (0.7)</td>
<td>2.9 (1.8-4.4)</td>
<td>3.5 (2.2-5.4)</td>
<td>***</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>L63</td>
<td>35 (1.2)</td>
<td>3.8 (2.7-5.4)</td>
<td>3.9 (2.8-5.5)</td>
<td>***</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>K50</td>
<td>29 (1.0)</td>
<td>2.5 (1.7-3.5)</td>
<td>3.4 (2.4-4.9)</td>
<td>***</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>K51</td>
<td>27 (0.9)</td>
<td>1.5 (1.0-2.3)</td>
<td>2.2 (1.5-3.2)</td>
<td>***</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>I10</td>
<td>280 (9.5)</td>
<td>0.5 (0.4-0.5)</td>
<td>2.2 (1.9-2.6)</td>
<td>***</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>I70</td>
<td>12 (0.4)</td>
<td>0.7 (0.4-1.2)</td>
<td>3.5 (1.9-6.2)</td>
<td>***</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>I63</td>
<td>25 (0.8)</td>
<td>0.7 (0.5-1.1)</td>
<td>3.0 (2.0-4.6)</td>
<td>***</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>I20</td>
<td>31 (1.1)</td>
<td>0.5 (0.3-0.7)</td>
<td>1.9 (1.3-2.8)</td>
<td>***</td>
</tr>
<tr>
<td>Disorders of lipoprotein metabolism and other lipidemias</td>
<td>E78</td>
<td>167 (5.7)</td>
<td>0.4 (0.4-0.5)</td>
<td>1.8 (1.5-2.2)</td>
<td>***</td>
</tr>
<tr>
<td>Obesity</td>
<td>E66</td>
<td>253 (8.6)</td>
<td>1.1 (0.9-1.2)</td>
<td>1.6 (1.4-1.9)</td>
<td>***</td>
</tr>
<tr>
<td>Problems related to lifestyle</td>
<td>Z72</td>
<td>138 (4.7)</td>
<td>0.9 (0.8-1.1)</td>
<td>1.5 (1.3-1.8)</td>
<td>***</td>
</tr>
<tr>
<td>Depressive episode</td>
<td>F32</td>
<td>364 (12.4)</td>
<td>1.1 (0.9-1.2)</td>
<td>1.4 (1.3-1.6)</td>
<td>***</td>
</tr>
<tr>
<td>Other anxiety disorders</td>
<td>F41</td>
<td>502 (17.0)</td>
<td>1.3 (1.1-1.4)</td>
<td>1.5 (1.4-1.7)</td>
<td>***</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>F42</td>
<td>42 (1.4)</td>
<td>2.3 (1.7-3.1)</td>
<td>2.0 (1.5-2.7)</td>
<td>***</td>
</tr>
<tr>
<td>Non-organic sleep disorder</td>
<td>F51</td>
<td>296 (10.0)</td>
<td>0.9 (0.8-0.9)</td>
<td>1.5 (1.4-1.8)</td>
<td>***</td>
</tr>
<tr>
<td>Sleep-disorders</td>
<td>G47</td>
<td>256 (8.7)</td>
<td>0.9 (0.9-1.1)</td>
<td>1.8 (1.6-2.0)</td>
<td>***</td>
</tr>
<tr>
<td>Other bacterial intestinal infections</td>
<td>A04</td>
<td>31 (1.1)</td>
<td>1.7 (1.2-2.4)</td>
<td>2.4 (1.7-3.4)</td>
<td>***</td>
</tr>
<tr>
<td>Erysipelas</td>
<td>A46</td>
<td>95 (3.2)</td>
<td>1.5 (1.2-1.8)</td>
<td>3.4 (2.8-4.2)</td>
<td>***</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>A69.2</td>
<td>140 (4.8)</td>
<td>1.1 (0.9-1.3)</td>
<td>1.7 (1.4-2.0)</td>
<td>***</td>
</tr>
<tr>
<td>Herpes simplex infections</td>
<td>B00</td>
<td>145 (4.9)</td>
<td>3.2 (2.7-3.8)</td>
<td>3.3 (2.8-3.9)</td>
<td>***</td>
</tr>
<tr>
<td>Viral infection of unspecified site</td>
<td>B34</td>
<td>977 (33.2)</td>
<td>2.1 (2.0-2.3)</td>
<td>1.6 (1.5-1.7)</td>
<td>***</td>
</tr>
<tr>
<td>Dermatophytosis</td>
<td>B35</td>
<td>236 (8.0)</td>
<td>1.8 (1.5-2.0)</td>
<td>2.5 (2.2-2.8)</td>
<td>***</td>
</tr>
<tr>
<td>Candidias</td>
<td>B37</td>
<td>253 (8.6)</td>
<td>1.7 (1.5-1.9)</td>
<td>2.1 (1.8-2.4)</td>
<td>***</td>
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<tr>
<td>Streptococcus and staphylococcus as the cause of diseases classified to other chapters</td>
<td>B95</td>
<td>75 (2.5)</td>
<td>2.5 (2.1-3.3)</td>
<td>5.9 (4.6-7.4)</td>
<td>***</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>ICD-10-code</td>
<td>Atopic dermatitis (n=2946) n (%)</td>
<td>OR (95 % CI)</td>
<td>Adjusted OR # (95% CI)</td>
<td>Significance level ##</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------------------------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Impetigo</td>
<td>L01</td>
<td>585 (19.9)</td>
<td>8.0 (7.3-8.8)</td>
<td>4.9 (4.5-5.4)</td>
<td>***</td>
</tr>
<tr>
<td>Resistance to methicillin</td>
<td>U82.1</td>
<td>21 (0.7)</td>
<td>3.7 (2.4-5.7)</td>
<td>2.9 (1.9-4.5)</td>
<td>***</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Z72.0</td>
<td>66 (2.2)</td>
<td>0.9 (0.7-1.1)</td>
<td>1.5 (1.2-2.0)</td>
<td>***</td>
</tr>
<tr>
<td>Cerebral atherosclerosis</td>
<td>I67.2</td>
<td>1 (0.0)</td>
<td>3.9 (0.5-28.9)</td>
<td>15.3 (2.1-114.1)</td>
<td>**</td>
</tr>
<tr>
<td>Chronic ischemic heart disease</td>
<td>I25</td>
<td>48 (1.6)</td>
<td>0.4 (0.3-0.5)</td>
<td>2.0 (1.3-2.8)</td>
<td>**</td>
</tr>
<tr>
<td>Scabies</td>
<td>B86</td>
<td>37 (1.3)</td>
<td>2.2 (1.6-3.1)</td>
<td>1.6 (1.2-2.2)</td>
<td>**</td>
</tr>
<tr>
<td>Other specified bacterial agents as the cause of diseases classified to other chapters</td>
<td>B96</td>
<td>29 (1.0)</td>
<td>0.7 (0.5-0.9)</td>
<td>1.7 (1.2-2.5)</td>
<td>**</td>
</tr>
<tr>
<td>Arthritis</td>
<td>M05-M09</td>
<td>32 (1.1)</td>
<td>1.0 (0.7-1.5)</td>
<td>2.0 (1.4-2.8)</td>
<td>**</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>K90.0</td>
<td>34 (1.2)</td>
<td>1.7 (1.2-2.5)</td>
<td>1.7 (1.2-2.4)</td>
<td>**</td>
</tr>
<tr>
<td>Lack of physical exercise</td>
<td>Z72.3</td>
<td>12 (0.4)</td>
<td>1.4 (0.8-2.4)</td>
<td>2.1 (1.2-3.8)</td>
<td>**</td>
</tr>
<tr>
<td>Hyperkinetic disorder</td>
<td>F90</td>
<td>125 (4.2)</td>
<td>1.8 (1.5-2.2)</td>
<td>1.3 (1.1-1.5)</td>
<td>**</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>F50</td>
<td>36 (1.2)</td>
<td>2.5 (1.8-3.4)</td>
<td>1.6 (1.1-2.2)</td>
<td>**</td>
</tr>
<tr>
<td>Streptococcal sepsis</td>
<td>A40</td>
<td>3 (0.1)</td>
<td>1.4 (0.4-4.3)</td>
<td>3.9 (1.3-12.3)</td>
<td>*</td>
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<tr>
<td>Meningococcal infection</td>
<td>A39</td>
<td>1 (0.0)</td>
<td>9.0 (1.2-67.9)</td>
<td>12.9 (1.6-101.7)</td>
<td>*</td>
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<tr>
<td>Pneumonia due to Streptococcus pneumonia</td>
<td>J13</td>
<td>4 (0.2)</td>
<td>1.3 (0.5-3.6)</td>
<td>3.2 (1.2-8.5)</td>
<td>*</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>E10</td>
<td>32 (1.1)</td>
<td>0.9 (0.6-1.3)</td>
<td>1.5 (1.1-2.2)</td>
<td>*</td>
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<tr>
<td>Type 2 diabetes mellitus</td>
<td>E11</td>
<td>71 (2.4)</td>
<td>0.4 (0.3-0.5)</td>
<td>1.3 (1.0-1.7)</td>
<td>*</td>
</tr>
<tr>
<td>Other sepsis</td>
<td>A41</td>
<td>9 (0.3)</td>
<td>0.6 (0.3-1.2)</td>
<td>2.0 (1.0-3.9)</td>
<td>*</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>K209A</td>
<td>2 (0.1)</td>
<td>2.9 (0.7-12.0)</td>
<td>3.9 (0.9-15.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Autism</td>
<td>F84.0/F84.1</td>
<td>40 (1.4)</td>
<td>1.9 (1.4-2.6)</td>
<td>1.2 (0.9-1.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>G35</td>
<td>3 (0.1)</td>
<td>0.5 (0.2-1.5)</td>
<td>0.7 (0.2-2.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>M32</td>
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<td>0.9 (0.2-3.5)</td>
<td>1.3 (0.3-5.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>I21</td>
<td>10 (0.3)</td>
<td>0.3 (0.2-0.5)</td>
<td>1.1 (0.6-2.1)</td>
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</tr>
<tr>
<td>Subsequent myocardial infarction</td>
<td>I22</td>
<td>0 (0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-0.0)</td>
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</tr>
<tr>
<td>Certain current complications following acute myocardial infarction</td>
<td>I23</td>
<td>0 (0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-0.0)</td>
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<tr>
<td>Other acute ischaemic heart disease</td>
<td>I24</td>
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<td>0.0 (0.0-0.0)</td>
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<tr>
<td>Smoking</td>
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<td>1.3 (0.9-1.7)</td>
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<tr>
<td>Alcohol use</td>
<td>Z72.1</td>
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<td>0.9 (0.3-3.0)</td>
<td>2.0 (0.6-6.3)</td>
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<tr>
<td>Comorbidity</td>
<td>ICD-10-code</td>
<td>Atopic dermatitis (n=2946) n (%)</td>
<td>OR (95% CI)</td>
<td>Adjusted OR * (95% CI)</td>
<td>Significance level ##</td>
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<td>-------------</td>
<td>------------------------</td>
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</tr>
<tr>
<td>Schizophrenia</td>
<td>F20</td>
<td>2 (0.1)</td>
<td>0.3 (0.1-1.1)</td>
<td>0.5 (0.1-2.0)</td>
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<tr>
<td>Other sexually transmitted chlamydial disease</td>
<td>A56</td>
<td>60 (2.0)</td>
<td>1.7 (1.4-2.3)</td>
<td>1.2 (0.9-1.5)</td>
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<tr>
<td>Tuberculosis of skin and subcutaneous tissue</td>
<td>A18.4</td>
<td>0 (0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV) disease</td>
<td>B20</td>
<td>0 (0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-0.0)</td>
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</tr>
<tr>
<td>Cytomegaloviral disease</td>
<td>B25</td>
<td>3 (0.1)</td>
<td>2.5 (0.8-7.8)</td>
<td>2.8 (0.9-8.7)</td>
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<tr>
<td>Anogenital herpesviral (herpes simplex) infection</td>
<td>A60</td>
<td>18 (0.6)</td>
<td>1.6 (1.0-2.5)</td>
<td>1.4 (0.9-2.2)</td>
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<tr>
<td>Other diseases caused by chlamydiae</td>
<td>A74</td>
<td>10 (0.4)</td>
<td>1.2 (0.6-2.1)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Gonococcal infection</td>
<td>A54</td>
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<td>1.6 (0.4-6.5)</td>
<td>1.5 (0.4-5.9)</td>
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<tr>
<td>Viral agents as the cause of diseases classified to other chapters</td>
<td>B97</td>
<td>5 (0.2)</td>
<td>1.3 (0.5-3.1)</td>
<td>1.4 (0.6-3.3)</td>
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</tr>
<tr>
<td>Tick-borne viral encephalitis</td>
<td>A84</td>
<td>0 (0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>0.0 (0.0-0.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>B15-B18</td>
<td>5 (0.2)</td>
<td>0.4 (0.2-0.9)</td>
<td>0.5 (0.2-1.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Malignant melanoma of skin</td>
<td>C43</td>
<td>8 (0.3)</td>
<td>0.6 (0.3-1.1)</td>
<td>1.5 (0.7-3.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Other malignant neoplasms of skin</td>
<td>C44</td>
<td>28 (1.0)</td>
<td>0.4 (0.2-0.5)</td>
<td>1.3 (0.9-1.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>C81-C86</td>
<td>4 (0.1)</td>
<td>0.7 (0.3-1.9)</td>
<td>1.9 (0.7-5.2)</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Odds ratio adjusted for age group and sex

## Significance level of adjusted odds ratio (* p<0.05; ** p<0.01; *** p<0.001; ns p>0.05).
and further studies are needed on large groups. The comor -
pared to the global population cannot easily be explained
prevalence of OCD in the population of Jönköping com-
the control group (0.6%). The reason for the generally lower
global prevalence, but it was significantly less prevalent in
diagnosed with OCD, which correlates somewhat with the
during our test period of nine years, 1.4% of the AD patients were
diagnosed with OCD which makes studies on additional and
preferably larger populations essential to further investigate
the association.

OCD is characterized by recurrent thoughts, urges or im-
ages that lead to repetitive behavior or mental acts, causing
distress and anxiety. These are severely time-consuming and/or
cause impairment in social, occupational or other important
situations [24]. The estimated one-year prevalence of
OCD is 1.2% and the estimated lifetime prevalence is 2.3%,
with an onset usually seen before the age of 30 [25]. During
our test period of nine years, 1.4% of the AD patients were
diagnosed with OCD, which correlates somewhat with the
global prevalence, but it was significantly less prevalent in
the control group (0.6%). The reason for the generally lower
prevalence of OCD in the population of Jönköping com-
pared to the global population cannot easily be explained
and further studies are needed on large groups. The comor-
bidities most often seen with OCD are additional psychiatric
disorders [26].

Previous studies and reviews investigated the role of the
immune system in the pathophysiology of OCD [27-29].
There is some evidence that persistent low-grade inflamma-
tion is seen in OCD patients [28]. Specifically, the cytokines
IL-4 and IL-17 are elevated in both AD and OCD [30-32].
Autoantibodies against the basal ganglia are almost five
times more likely to be detected in patients with OCD com-
pared to controls. In some cases of OCD infectious agents,
such as streptococcus, other bacteria, viruses and parasites
are seen as triggers of autoimmunity [28]. In some children,
the onset or exacerbation of OCD is seen in association with
Streptococcus A infection. The condition is named pediat-
ric autoimmune neuropsychiatric disorder associated with
group A streptococci (PANDAS). Hypothetically, Streptococ-
cus A triggers an autoimmune reaction that interacts with
neurons in the basal ganglia and causes OCD [33].

The above-mentioned studies suggest that a dysregulated
inflammatory response might contribute to the occurrence of
OCD and this could potentially explain the association
with AD. Furthermore, if microbes can trigger autoimmu-
nity that leads to OCD, it is not irrelevant to consider in-
creased skin infection in AD as a possible risk factor for
OCD. A total-population-based Swedish study found a sig-
nificant association between OCD and several autoimmune
diseases including psoriasis vulgaris (32%). However, AD
was not included in the study. The authors evaluated the risk
of 40 autoimmune diseases in people with OCD and their
relatives and found an increased risk for autoimmune dis-
 ease in first-degree relatives to patients with OCD compared
to second- and third-degree relatives. Their results suggest a
potential genetic link between OCD and autoimmune dis-
eases[34]. Similar studies could be performed with OCD and
AD to see if there are indications of genetic linkage between
the two diseases.

In conclusion, the two conditions likely share several
common gene-environmental pathways. Optimized treat-
ment of AD to restore the skin barrier and prevent skin infec-
tions might be of great importance in order to prevent
OCD. For future research, larger populations should be in-
cluded and it should be investigated if those with both AD
and OCD also have been diagnosed with PANDAS and if
they have other autoimmune diseases or infections in close
temporal association with the onset of OCD. The connec-
tion should be adjusted for comorbidity diagnoses shared
between AD and OCD, such as anxiety disorder and depres-
sion. Studies to see if OCD and AD share genetic material/activated gene sequences could also be interesting.

Depression and anxiety occurred more frequently in pa-
tients with AD compared to the control population, which
was in line with earlier findings. Sleep disturbance was in-
creased in AD patients in this study. Sleep disturbance, pru-
ritus, stigma, social isolation and poor quality of life are
associated with AD and might contribute to this correlation
[9, 35, 36]. Pruritus and inflammation as part of AD can lead
to sleep disturbances which in turn may cause depression
and anxiety [9]. The systemic inflammation seen in AD is an-
other possible explanation for the connection since inflam-
matory proteins are elevated in depressed patients in blood
and cerebrospinal fluid [37-39]. Cytokines can affect neu-
rotransmission and behaviors and emotions associated with
both sickness and depression [40].

This study found that ADHD was significantly in-
creased in the AD group which is in line with previous
studies [41, 42]. Most of these studies however include only
children or analyze children and adults separately [19-21].
Buske-Kirschbaum et al propose three different explanations
for the association between AD and ADHD: 1) Allergic in-
flammation and psychologic stress due to chronic disease
leads to the release of inflammatory cytokines that interfere
with the maturation of prefrontal cortex regions and neuro-
transmission involved in ADHD pathology; 2) elevated stress
levels in ADHD trigger AD or 3) the conditions are separate but have shared risk factors (e.g. genetics, prenatal stress) that increase the risk of developing both disorders [43].

Similar to previous studies we saw increased risk for a number of infections and autoimmune diseases in the AD group. Somewhat surprisingly, we found an increase in Lyme disease in the AD group which logically cannot be explained by a default skin barrier. Literature is scarce on the area and future studies on the connection and potential co-factors, such as neuroborreliosis, could be interesting.

The positive association between AD and Crohn’s disease, ulcerative colitis, celiac disease, alopecia areata and vitiligo detected in this study, correlates well with previous study results [8, 13, 44]. Inflammatory bowel disease, psoriasis and alopecia areata share several genetic risk loci with AD [45-47]. A German cohort study showed an increased risk of rheumatoid arthritis and inflammatory bowel disease (and a decreased risk for type 1 diabetes) in combination with AD, independent of known risk alleles [48]. Elevated levels of Th1, Th2 and Th17 responses are present in the pathogenesis of both inflammatory bowel disease and atopic dermatitis [10, 49].

We found a significant association with several comorbidities that can be categorized as cardiovascular disease. Four well-known risk factors for cardiovascular disease were also increased in the AD group, e.g. hyperlipidemia, obesity, hypertension and diabetes. Poor health behavior is often seen in patients with AD. They have a higher incidence of smoking, drinking alcohol at a young age and have reduced physical activity. Children with AD participate less in sports and play more videogames [50, 51]. This was to some extent reflected in our results. These combined increased cardiovascular risk factors, as well as the aforementioned frequent sleep disturbance in patients with AD, likely play an important role in the development of cardiovascular disease in the AD population [7]. The systemic inflammation seen in AD and to some extent in cardiovascular disease as well as in some of the cardiovascular risk factors might be one reason for the association, as well as genetic factors [52, 53]. Two studies however found an increased risk for cardiovascular disease and stroke in AD patients initially but not after adjusting for cardiovascular risk factors, which suggests that poor health behavior and cardiovascular risk factors are the major reason for increased cardiovascular disease in AD patients, rather than systemic inflammation [54, 55]. We did not choose to adjust for cardiovascular risk factors when analyzing the odds ratio for cardiovascular disease. Thus this study does not contribute to deeper insight into the mechanism for the connection between such conditions and AD. Generally, cardiovascular risk factors are seen less often in association with AD compared to psoriasis [56].

This study has several strengths. We used an electronic medical record for the collection of all data. These records allowed easy access to data that was required for the analysis. This furthermore enabled a large study population. We chose to only include patients in the study group that received their AD diagnosis in the Dermatology or Pediatric Clinic. At these clinics, physicians have more specialized competence to correctly recognize these conditions than in other clinics. Understandably, this means that those with an AD diagnosis from another clinic were included in the control group rather than the study group, as were those who received an AD diagnosis before and not during the test period. Most probably, the patients in our study group have a moderate to severe degree of disease and most of the AD diagnoses included in the control group have mild symptoms. This can affect the results in different ways. It might make significant associations between AD and the different comorbidity more difficult since those with one of the examined comorbidities in the control group might have AD. If that is the case, then that would mean that their exclusion from the control group would make our results even more significant. On the other hand, it could be speculated that comorbidity is mostly seen in moderate to severe AD, which strengthens the choice of inclusion criteria. A limitation of this study was that we did not specify the degree of AD symptoms, so we are not able to analyze disease severity and how it correlates to comorbidity. Another limitation is that we initially only adjusted for age and gender. As discussed above, metabolic diseases share risk factors with some common comorbidity in AD. Unless we adjust for those risk factors nothing can be said about a causal association between cardiovascular comorbidity and AD. The connection between AD and OCD should be adjusted for shared comorbidity. In agreement with the current literature, we found an increased risk for allergic rhinitis, allergic asthma and atopic conjunctivitis in AD patients. This is in line with previous knowledge and can be used as validation of the diagnostic code for AD [5]. We did not choose to validate every comorbidity diagnosis since this study was intended as a screening for multiple comorbidities in order to detect interesting correlations.

Conclusions

Our results strengthen the knowledge that a wide spectrum of comorbidity is seen in AD. We found an increased risk between AD and OCD. These findings are essential for clinicians seeing patients with AD. Early detection and treatment of OCD are crucial for optimal treatment of AD and the quality of life of AD patients. Future nationwide studies are needed to confirm our results.
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What do Patients Want to See on Social Media? Evidence From a Two-Year Experiment

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Key words: social media, internet, acne, health promotion, education

Citation: Barrutia L, Vega-Gutiérrez J, Santamarina-Albertos A. What do patients want to see on social media? Evidence from a two-year experiment. Dermatol Pract Concept. 2023;13(1):e2023020. DOI: https://doi.org/10.5826/dpc.1301a20

Accepted: April 11, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Dermatological information on social media is dominated by misleading and potentially harmful content from nonexperts. Literature suggests that, to address this issue, dermatologists should develop an online presence. However, the successful presence of dermatologists on social media has been criticized for focusing on cosmetic dermatology and not representing the broad spectrum of the specialty.

Objectives: The aim of this study was to systematically analyze which dermatological topics interest the public most, and to find out whether it is feasible for a dermatologist to become influential on social media while presenting all dermatological topics equally.

Methods: The study was performed on an educational dermatology YouTube channel. The 101 videos published in a two-year period were divided into cosmetic (51 videos) and medical dermatology (50 videos). Student's t-test was conducted to determine whether there were significant differences in views. Medical dermatology videos were then classified into three categories: Acne, facial dermatoses (excluding acne) and other dermatological diseases. A Kruskal-Wallis test was used to compare these three categories and cosmetic dermatology.

Results: When comparing cosmetic and medical dermatology, no significant differences were found. When comparing the four categories, cosmetic dermatology and acne were found to generate significantly more views than other dermatological diseases.

Conclusions: The public seems to be particularly interested in cosmetic dermatology and acne. This might make it challenging to become successful on social media while presenting a balanced portrayal of dermatology. However, focusing on popular topics can provide a real chance to be influential and protect vulnerable people from misinformation.
Introduction

Dermatological information on social media is dominated by misleading and potentially harmful content from nonexperts [1,2]. An analysis of Instagram hashtags [3] found that most top dermatology-related posts are made by individuals without formal dermatology training. A study [4] on the quality of YouTube videos about psoriasis classified 63% of videos as misleading or dangerous. Many other studies [5-8] have noted a vast amount of inaccurate or low-quality dermatological information on different social media platforms.

This problem primarily affects vulnerable people, such as adolescents and young adults, who are the most active users of these platforms [2,9,10]. It has been suggested that in order to address this issue, dermatologists should develop an online presence [5,11-13]. However, dermatologists’ participation in social media is a new phenomenon, and the extant literature offers little insight into how dermatologists can develop a successful social media presence. One exception is a study by Sierro et al. [11], which identified the top 10 dermatology influencers on social media and found that 83% of the content they produced focused on cosmetic dermatology. According to Sun et al. [12], this finding might lead to the public perception that dermatologists spend the majority of their time treating conditions with modest morbidity, which is inconsistent with reality. They highlighted the need to dispel this misconception and create content on a wide variety of dermatological diseases from both clinical and histological perspectives [12]. Guzman and Barbieri [1] shared this concern and noted that the presence of dermatologists on social media is limited in comparison with non-dermatologist sources, which are prone to bias and misinformation. Similarly, Green and Britten [14] argued that dermatologists should create content showcasing, in a balanced manner, the broad spectrum of dermatology by presenting interesting medical cases, dermoscopic and histologic images, or commentaries on medical literature.

Therefore, the successful presence of dermatologists on social media remains limited and has been criticized for focusing on cosmetic dermatology as opposed to accurately representing the role of dermatologists [1,12,13]. In this context, this study examined a research question that has not been systematically addressed in the literature: Is it feasible for a dermatologist to develop a relevant presence on social media while equally representing all dermatological topics?

Objectives

The emergence and prevalence of social media is a relatively new and unknown phenomenon. Probably the best way to understand new phenomena is to explore them as an insider [14]. Consequently, there is a need for insider research exploring how the public reacts to the presentation of various dermatological topics by dermatologists. Accordingly, the aim of this research is to determine from the inside which dermatological topics social media users find most interesting. This analysis will allow us to deduce whether it is feasible for a dermatologist to become influential on social media while presenting all dermatological topics with equal prominence, as suggested from a conceptual perspective [1,12,14].

Methods

Study Design

Most previous contributions on dermatology in social media have relied on conceptual developments and secondary sources. This is distinct from the tradition of dermatologic research, which has mostly relied on primary sources (i.e., everyday practice). The present study is based on the direct experience of a dermatologist on social media over a two-year period.

In October 2019, one of the authors launched an educational dermatology YouTube channel. The channel was designed to avoid the risks and ethical challenges that social media involves for dermatologists [15]. The channel did not include sponsored or personal content, and videos followed the DISCERN quality criteria [9]. References to relevant scientific literature were provided, individual consultations were not answered, and viewers were encouraged to consult a dermatologist. While commercial products were shown because of strong demand from subscribers, product assessments relied on effectiveness. No commercial agreements were established. A new video was launched weekly, and following a two-year period, the channel had over 134,000 subscribers and 5.5 million views. In total, 101 videos were posted about a wide variety of dermatological topics including acne and acne scars, rosacea, melasma, hiradenitis suppurativa, psoriasis, vitiligo, hair loss, atopic dermatitis, seborrheic dermatitis, nevi, sun protection, melanoma, basal cell carcinoma, squamous cell carcinoma, polymorphous light eruption, hyperhidrosis, folliculitis, laser hair removal, keratosis pilaris, post-inflammatory hyperpigmentation, dermatological treatments such as benzoyl peroxide and isotretinoin, skin type, medical peeling, botulinum toxin, and active ingredients in cosmetics.

All videos were presented by the same dermatologist in the same setting and followed a similar approach. They were also similar in terms of duration and aesthetic design. We can assume, therefore, that the differences in the average daily video views were mostly due to varying public interest in the topics covered.

Data Collection and Overview of Channel Analytics

Data were collected from YouTube Studio, a platform provided by YouTube to help content creators manage their
channels. YouTube Studio provides key channel analytics to better understand video and channel performance. This research focuses on a specific metric: average daily views (i.e., views/days since upload). Other metrics provided by YouTube Studio include subscribers, watch time (hours), likes, dislikes, and shares. All videos posted from 25 October 2019 to 25 October 2021 were included in the study.

Statistical Analysis

Statistical analysis was performed using Stata 16 (StataCorp LLC). We categorized the videos according to the topic covered and analyzed whether there were significant differences in average daily views depending on the video category.

To categorize the videos under study, we followed a two-step approach. In the first step, we grouped the videos into two broad categories: cosmetic dermatology (51 videos) and medical dermatology (50 videos). We conducted a Student’s t-test to determine whether there were significant differences between the views counted for both types of videos. Despite the absence of normality in our data, the relatively large number of observations in both categories (n = 50 and n = 51, respectively) led us to use the parametric Student’s t-test [16].

In the second step, we created several subgroups among the medical videos. Subcategorization was performed because it was apparent that there was great variance in the views within this category. Specifically, we divided the medical videos into three subgroups: acne; facial dermatoses, excluding acne; and other dermatological diseases. This arrangement was based on our empirical observations. Overall, we observed that acne and, to a lesser extent, other facial dermatoses, such as rosacea and melasma, generated more views than other dermatological diseases. This may be because self-care is erroneously considered feasible for these conditions. Additionally, facial dermatoses are highly visible, with substantial social repercussions [17-19]. We established an individual category for acne because of its particularly high prevalence and because it markedly affects adolescents and young adults, who comprise YouTube’s largest user base [2,9,10]. We then performed a non-parametric Kruskal-Wallis rank test to compare the three medical categories and cosmetic videos. This non-parametric test was chosen due to the absence of normality in our data and the relatively scarce number of videos in some categories [16].

The videos had been published on different dates, which implies that they had had different opportunities to be viewed. Therefore, the videos were not compared in terms of total views but in terms of average daily views [20].

Results

Videos on acne had the highest average daily views (268.66), followed by those on cosmetic dermatology (255.49) and other facial dermatoses (160.18). Videos on other dermatological diseases had the lowest average daily views (91.61).

Student’s t-test determined that there were no significant differences between views of cosmetic dermatology and medical dermatology videos, even though the cosmetic videos had more views on average (p = .1511).

The Kruskal-Wallis rank test, which compared the three medical categories and cosmetic videos, showed that videos on acne and cosmetic dermatology received significantly more views than those on other dermatological diseases (p = .0028 and p = .0005, respectively). There was a marginally significant difference (p = .0533) between views of videos on other facial dermatoses and those on other dermatological diseases. No significant differences were found between cosmetic dermatology and acne (p = .2392), cosmetic dermatology and other facial dermatoses (p = .5493), and acne and other facial dermatoses (p = .1266) (see Table 1).

While this research focused on comparing average daily video views, other engagement analytics may add information about the qualitative perceptions of the public on a YouTube channel conducted by a dermatologist. The two-year period under study led to 221,993 likes, 47,162 shares, and 17,815 comments (see Table 2).

To evaluate the degree of goodness of these channel analytics, we used a study on 104,899 YouTube accounts and classified them as poor, average, or good [21]. Metrics scoring at the 60th percentile or higher were considered good. Specifically, the study considered the following engagement analytics:

1. Like-to-dislike rate (i.e., percentage of number of likes over the sum of likes and dislikes);
2. Views-to-subscriber ratio (i.e., number of views over number of subscribers);
3. Comments-to-views rate (i.e., percentage of users who have watched the video and commented on it); and
4. Likes-to-view rate (i.e., percentage of users who have watched the video and explicitly stated that they liked it).

When these metrics were applied to the channel, we observed that in all cases, the channel was above the threshold level required to be considered good. First, the like-to-dislike rate was 98.6% (> 97.4%). Second, the views-to-subscriber ratio was 41.01 (> 33.1). Third, the comments-to-views rate was .32% (> .04%). Lastly, the like-to-view rate was 4.03 (> 3.72). Most comments were highly positive. Many users recognized the value of the knowledge conveyed through the channel and were highly appreciative that a dermatologist had offered evidence-based knowledge on social media.
Therefore, it is essential that dermatologists share evidence-based information on appropriate sun safety attitudes to educate the population and fight misinformation. Several studies have shown that social media can be a cost-effective way to disseminate awareness on this topic, and dermatological associations, such as the National Academy of Sciences’ Interdisciplinary Perspectives on Skin Cancer, have concluded that there is a need to promote sun protection in children and young adults on these platforms.

Other examples of non-popular dermatological diseases that could be addressed on social media include chronic inflammatory skin conditions, such as psoriasis or hidradenitis suppurativa. Several studies have shown that social media can be a cost-effective way to disseminate awareness on these topics.

Discussion and Conclusions

Our findings show that public concerns focus on acne and cosmetic dermatology and that viewers are not equally interested in all dermatological topics. Therefore, it might be difficult to become successful on social media and ensure visibility while presenting a balanced portrayal of our specialty. This represents an important challenge for dermatologists because some topics, despite being less popular, need to be addressed due to their importance, such as skin cancer and its prevention. The literature shows that most videos about tanning on YouTube portray it positively, and that there are more advertisements for tanning salons than the total number of videos portraying the dangers of tanning [22-24]. Therefore, it is essential that dermatologists share evidence-based information on appropriate sun safety attitudes to educate the population and fight misinformation [25-27]. Several studies have shown that social media can be a cost-effective way to disseminate awareness on this topic, and dermatological associations, such as the National Academy of Sciences’ Interdisciplinary Perspectives on Skin Cancer, have concluded that there is a need to promote sun protection in children and young adults on these platforms [30].

Other examples of non-popular dermatological diseases that could be addressed on social media include chronic inflammatory skin conditions, such as psoriasis or hidradenitis suppurativa. Several studies have shown that...
patient education through social media improves the quality of life of patients with these diseases. Consequently, dermatologists face the difficult challenge of finding a balance between prioritizing popular topics and not disregarding others that may have an important impact on people’s well-being.

While keeping this balance in mind, we believe that prioritizing the topics that people want to see (i.e., acne and cosmetic dermatology) can have the next three benefits for dermatologists and society as a whole: (1) ensuring visibility, (2) having a positive, evidence-based influence on dermatological culture and health-related decisions, and (3) having a real option to convey a complete portrayal of dermatological topics (albeit with unequal prominence).

First, to ensure visibility, YouTube videos must be promoted by the YouTube algorithm. While the operation of the algorithm is a black box, it seems to favor content that is viewed more frequently by users (i.e., what users, through their behavior, have revealed they want to see) [21]. This mechanism makes it extremely difficult to garner public influence while presenting topics that the public does not usually search for on YouTube.

Second, focusing on what people want to see provides dermatologists with a real opportunity to have a positive, evidence-based influence on people’s culture and behavior. Comments on videos about popular topics illustrate that they can help foster important dermatological culture that extends beyond the focal topic: “Since watching your videos, I use sunscreen regularly.” In particular, focusing on acne can lead to increased visibility among adolescents [9,10]. This can facilitate the dissemination of important dermatological habits, such as sun protection, from a young age, aiding in skin cancer prevention [26,29,33,34]. Therefore, focusing on popular topics can be a way to convey important messages about other important dermatological issues. Schneiderbanger et al. [35] presented an interesting example of how dermatologists’ concerns about a disease (skin cancer) can be associated with the main interests of young females (skin aging). Since the prevention of skin aging seems to be an important concern among young females, a dermatologist could broadcast a video emphasizing the association between tanning and premature skin aging, thus helping discourage this behavior and, therefore, contributing to reducing the prevalence of skin cancer [35]. Consequently, dermatologists can create content about topics that concern users and use it to convey additional skin health advice in a compelling way.

Third, focusing on people’s interests serves to gain subscribers and build loyalty [2]. Loyal subscribers tend to watch more channel videos, including those on less frequently searched dermatological content. Some video comments are illustrative of this: “I watch all your videos,” “I do not have vitiligo, but the video is interesting.” Therefore, videos on less popular topics receive more views than they would otherwise, thereby increasing the likelihood that the YouTube algorithm will promote them to other users. Consequently, focusing on popular topics can, in the end, facilitate the dissemination of accurate knowledge about the broad spectrum of dermatology.

Our results show an overall preference for topics related to facial dermatological issues. The commonality among acne, cosmetic dermatology, and other facial dermatoses is that they affect the face. Views on videos about these topics are significantly higher than those on videos about dermatological diseases that do not normally affect this body area, such as psoriasis, hyperhidrosis, or hidradenitis suppurativa. Because the face is the most visible body part, previous studies have found that skin diseases in this area can have a remarkable effect on patients’ self-esteem and a profoundly negative impact on quality of life [17-19]. As a consequence, it seems logical that users search for these topics more than for less noticeable dermatological diseases.

Previous research suggests that social media allows dermatologists to do social work of great significance, disseminating an evidence-based dermatological culture and influencing the habits of the most vulnerable people [10,25,26,29,33,36,37]. For this reason, many authors have encouraged dermatologists into more active participation on these platforms [5,11-13]. Previous literature on the topics that dermatologists should present on social media is very scarce, but it has been suggested in the context of other aspects of social media content that dermatologists should adapt their content to the population. For instance, Güder and Güder [5] focused on the language used and highlighted that in order to increase visibility, dermatologists should use words that are familiar to patients instead of technical terms. We consider that focusing on popular topics can be a successful strategy that follows a similar approach.

While dermatologists must share information on important topics, such as skin cancer, even at the expense of losing visibility, our findings indicate that prioritizing the goal of a balanced portrayal of dermatology is difficult to achieve in the real context of social media. This is so because meeting this goal implies trying to lead social media users to focus their attention on topics in which they have no or little interest. Disregarding this balance in favor of popular content, without completely neglecting other relevant dermatological topics, might be worthy for dermatologists in terms of accomplishing a very relevant social mission.

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Clinical Review of Mucosal Melanoma: The 11-Year Experience of a Referral Center

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Key words: mucosal melanoma, diagnosis, treatments, rare disease


Accepted: June 29, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction: Mucosal melanoma is a rare neoplasm. Late diagnosis is caused by occult anatomic sites and scarcity of symptoms. Novel biological therapies have now become available. Demographic, therapeutic and survival records on mucosal melanoma are scarce.

Objectives: To provide an 11-year retrospective clinical review of real-world data on mucosal melanomas managed in a tertiary referral center in Italy.

Methods: We included patients with histopathological mucosal melanoma diagnoses from January 2011 to December 2021. Data were collected until the last known follow-up or death. Survival analysis was performed.

Results: Among 33 patients, we found 9 sinonasal, 13 anorectal and 11 urogenital mucosal melanomas (median age 82, females 66.7%). Eighteen cases (54.5%) presented with metastasis (p<0.05).
Introduction

Melanoma is a malignant tumor arising from melanocytes [1]. Although melanocytes are mostly localized in the skin, their precursors reach also endodermal and ectodermal mucosae migrating from the neural crest [2]. Primary mucosal melanoma arises from mucosal membranes lining the head and neck (i.e., nasal and oral cavities), anorectal, vulvovaginal, and urinary tract in order of frequency [3,4]. The occult locations in which mucosal melanoma occurs preclude sun exposure as a predisposing risk factor; the etiologic factors driving tumorigenesis in mucosal melanoma have not been discovered yet [5]. Mucosal melanoma represents 0.03% of all cancer diagnoses and 0.8-3.7% of all melanomas [5,6], with a higher incidence in women than men; different gender incidence is mainly due to vulvovaginal neoplasia, which represents alone 18% of mucosal melanomas [1].

Most patients with mucosal melanoma are diagnosed in a metastatic stage because of the late occurrence of symptoms and the occult location of the primary tumor [7]. The most common symptoms in nasal cavity melanomas are unilateral nasal obstruction, mass lesion, and epistaxis while in the oral cavity symptoms such as swelling, ulceration, bleeding, pain, or tooth mobility can occur. Anorectal melanomas usually manifest with rectal bleeding, anorectal discomfort, or prolapse of the tumor mass. In vulvovaginal melanomas presenting symptoms are bleeding, vulvar mass, pruritus, pain or irritation, micturition discomfort, and discharge [4].

There is no universal staging system for mucosal melanomas. Head and neck mucosal melanomas are usually staged according to the American Joint Committee on Cancer (AJCC) criteria for head and neck cancer; vulvar melanoma can be staged following the AJCC criteria for cutaneous melanoma, while no staging criteria have been established for mucosal melanoma arising in the urethra, vagina, rectum, and anus [8].

Surgical excision with negative margins, which is the treatment of choice in mucosal melanomas, is often unfeasible because of an anatomically complex site of origin [7,9]. Patients with unresectable or metastatic mucosal melanomas can be treated with the same regimen proposed for cutaneous melanoma [10], although the frequency of common driver BRAF is low compared to the cutaneous counterpart (50% vs 3-5%), with reduced usefulness of targeted therapy [1]. Mutation of the KIT gene is detected in about 25% of mucosal melanomas [1]; to date, guidelines suggest KIT testing only when BRAF and, eventually, NRAS, mutational status have been established; KIT targeted therapy is usually administered as a second line therapy [8]. In the last few years, immune checkpoint inhibitors (ICIs) have become a preferred first-line approach for patients with advanced or metastatic cutaneous melanoma. A recent review [7] showed that anti-CTLA-4 antibody ipilimumab has less efficacy as monotherapy than monoclonal antibodies targeting the PD-1 and PD-L1, which have proven more effective in the treatment of MMs, with prolonged survival and acceptable toxicity. A sub-analysis of mucosal melanomas performed in a five-year survival trial showed similar data on efficacy [8,11]. The treatment regimen currently authorized by Agenzia Italiana del Farmaco for advanced mucosal melanoma includes ipilimumab and anti-PD1 antibodies, while Imatinib is approved for unresectable metastatic melanoma in progression after immunotherapy [8].

As primary mucosal melanoma is an exceedingly rare neoplasm, demographic, histopathological, therapeutical, and survival records on this topic are scarce. The current study aims to provide an 11-year retrospective clinical review of the real-world data on mucosal melanomas managed in a tertiary referral center in Italy.
Methods

This was a retrospective study performed between 01/01/2011 to 31/12/2021. This study was approved by the Institutional Review Board of Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Italy (protocol number #2011/02347213).

We included consecutive patients with a histopathologically confirmed diagnosis of mucosal melanomas. We excluded recurrent tumors, unknown primary melanomas, and cases for which histological slides were not available for re-evaluation.

Data from the first clinical or instrumental diagnosis to the date of each patient’s last known follow-up appointment or death was obtained from digital medical records. We recorded patient age, gender, location of the lesion, presenting symptoms, site of metastasis at diagnosis if any (locoregional lymph node involvement, cerebral, visceral, or multiple metastases when more than one of the previous sites was involved) and histopathological and molecular features (cell morphology, Breslow thickness and ulceration when not compromised by fragmentation or orientation of biopsy specimen, and mutational status).

Surgery was recorded as debulking procedure or radical treatment. Systemic treatments were categorized according to current recommendations [8,10] as first-line biological treatment (nivolumab, pembrolizumab, or imatinib), as first-line chemotherapy when the patient was administered with systemic therapy in the pre-biological era, and as second-line treatments when therapy was switched to a different therapy because of disease progression. We also recorded if the patient underwent radiation therapy on the primary tumor, which was always managed with a cytoreductive-palliative purpose in our series [12].

Statistics

Statistical analysis was performed using STATA® software version 17 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). Descriptive statistics were presented for baseline demographic clinical characteristics for the entire group, as well as for the groups of patients with different locations. Continuous variables were presented as the number of patients (N), mean, standard deviation (SD), minimum (min), and maximum (max) and compared between subgroups using Unpaired Student's t-test; categorical variables were presented as frequency (N, percentage [%]) and compared using Pearson's chi-squared test. Survival analysis was performed using the Kaplan-Meier method and comparison between the survival curves was done using log-rank test. Univariate and multivariate analyses were done using the Cox-regression hazard model. Data from the univariate and multivariate regression analyses were expressed as Hazard ratio (HR) with it 95% confidence interval (CI). A p<0.05 was considered statistically significant.

Results

Demographic, Clinical, and Treatment Data

Among 33 patients with primary mucosal melanomas who were included in our analyses, we found 9 melanomas of the sinonasal region, 13 anorectal melanomas and 11 urogenital melanomas (of which 10 vulvovaginal melanomas and 1 bladder melanoma), as reported in Table 1 and Figure 1. Median age at diagnosis was 82 years (75-83), with no substantial differences by anatomical site. More women than men had mucosal melanoma (n= 22, 66.7%). Median follow-up period was 11.5 months.

Presenting symptoms for which physicians were consulted by the patient were recorded in Table 2 (in our series dermatologists, otolaryngologists, gynecologists, and endoscopists); most patients were then managed by the Skin Cancer Tumor Board.

We observed that 18 cases of mucosal melanoma (54.5%) out of 33 presented with metastasis at diagnosis (p<0.05) and that 91% and 66% of patients with anorectal and sinonasal melanomas had at least one metastatic site at diagnosis. In urogenital melanomas, 4 out of 11 (36.4%) showed metastases which were all diagnosed in locoregional lymph nodes (inguinofemoral nodes) and no distant metastases.

Surgery: Clinical records reported that 39.4% of patients underwent surgical treatment (p<0.05). All the sinonasal melanomas which were surgically managed (44.4%) underwent a debulking procedure, while every surgically managed anorectal and urogenital melanoma had a radical intent procedure (30.8% and 45.5%). Most patients did not undergo surgery because of metastasis at diagnosis (n=14), detection of different neoplasia at primary staging (n=2), unresectable tumor (n=3), age of the patient (n=1), death of the patient before surgery (n=1).

Systemic treatment: We identified 15 patients treated with systemic biological therapy as first-line treatment (p<0.05); 13 received nivolumab, 2 subjects were treated with pembrolizumab and 1 subject with imatinib. Only 1 patient received first-line chemotherapy (cyclophosphamide, vincristine, and dacarbazine combination treatment).

Furthermore, 5 patients were switched to a second-line systemic therapy; 3 of them were switched to ipilimumab, 1 to pembrolizumab and 1 to monotherapy with dacarbazine.

Radiation therapy (RT): in our analysis, RT on the primary tumor has always been proposed as a cytoreductive-palliative treatment; it was performed in all cases of sinonasal melanoma (p<0.05). Anorectal melanomas were treated with RT...
Table 1. Comparison of demographic, clinical, and survival data in patients with mucosal melanomas and stratification by the site of origin.

<table>
<thead>
<tr>
<th></th>
<th>Mucosal melanomas (n=33, 100%)</th>
<th>Sinunasal (n=9, 27.3%)</th>
<th>Anorectal (n=13, 39.4%)</th>
<th>Urogenital (n=11, 33.3%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median (IQR)</td>
<td>82 (75-85)</td>
<td>82 (75-83)</td>
<td>80 (72-87)</td>
<td>83 (80-85)</td>
<td>0.977</td>
</tr>
<tr>
<td>Female</td>
<td>22 (66.7)</td>
<td>5 (55.6)</td>
<td>11 (100)</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Metastasis at diagnosis</td>
<td>18 (54.5)</td>
<td>4 (44.4)</td>
<td>10 (76.9)</td>
<td>4 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>8 (24.2)</td>
<td>0 (0.0)</td>
<td>4 (30.8)</td>
<td>4 (36.4)</td>
<td>0.021</td>
</tr>
<tr>
<td>Visceral</td>
<td>4 (12.1)</td>
<td>3 (33.3)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Cerebral</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
<td>2 (15.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>≥2 sites</td>
<td>4 (12.1)</td>
<td>1 (11.1)</td>
<td>3 (23.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>13 (39.4)</td>
<td>4 (44.4)</td>
<td>4 (30.8)</td>
<td>5 (45.5)</td>
<td>0.015</td>
</tr>
<tr>
<td>Debulking</td>
<td>4 (12.1)</td>
<td>4 (44.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Radical excision</td>
<td>9 (27.3)</td>
<td>0 (0.0)</td>
<td>4 (30.8)</td>
<td>5 (45.5)</td>
<td></td>
</tr>
<tr>
<td>First-line biological therapy</td>
<td>17 (51.5)</td>
<td>5 (55.5)</td>
<td>6 (46.2)</td>
<td>5 (45.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>13 (39.4)</td>
<td>4 (44.4)</td>
<td>4 (30.8)</td>
<td>5 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2 (6.1)</td>
<td>1 (11.1)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>First-line chemotherapy</td>
<td>1 (3.0)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.253</td>
</tr>
<tr>
<td>Second-line systemic therapy</td>
<td>5 (15.1)</td>
<td>2 (22.2)</td>
<td>2 (15.4)</td>
<td>1 (9.1)</td>
<td>0.383</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>3 (9.1)</td>
<td>2 (22.2)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy on the primary tumor</td>
<td>17 (51.5)</td>
<td>9 (100)</td>
<td>6 (46.2)</td>
<td>2 (18.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Overall survival, median (IQR) months</td>
<td>11 (6-25)</td>
<td>14 (6-22)</td>
<td>6 (2-11)</td>
<td>26 (11-34)</td>
<td>0.021</td>
</tr>
<tr>
<td>Overall survival rate%, 12 months</td>
<td>71</td>
<td>55</td>
<td>54</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Overall survival rate%, 12 months</td>
<td>54</td>
<td>37</td>
<td>18</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Median follow-up period (months)</td>
<td>11.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

IQR: interquartile range

Figure 1. Flow diagram showing mucosal melanoma subdivided by anatomical site of origin.

Table 2. Presenting symptoms of mucosal melanoma by anatomical region.

<table>
<thead>
<tr>
<th>Site of primary melanoma</th>
<th>Presenting symptoms (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinonasal</td>
<td>Epistaxis (2), nasal obstruction (2), eyelid prosthesis (1)</td>
</tr>
<tr>
<td>Anorectal</td>
<td>Rectorrhagia (4), tumor mass prolapse (2), anemia (2)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Tumor mass (6), pigmentation of external genitalia (1), vaginal bleeding (1)</td>
</tr>
</tbody>
</table>

n= number(s)
in 46.3% of cases while only 2 patients with urogenital melanomas were treated with RT.

Survival data: Overall survival (OS), expressed as a median value, was longer in urogenital melanomas (26 months), than sinonasal melanomas (14 months) and anorectal melanomas (6 months).

As reported in the Kaplan-Meier estimate (Figure 2), sinonasal and anorectal melanoma carried higher mortality in the first two years; anorectal melanoma had a high mortality rate over time while sinonasal melanoma reached a plateau. Urogenital melanoma showed longer survival in the first two years from diagnosis with delayed mortality.

The 24-month overall survival rate among mucosal melanoma patients was 54%. The 24-month overall mortality for the location was 37% in sinonasal melanomas, 18% in anorectal melanoma and 100% in urogenital melanoma. The last observed exit from the estimate was 58 months (Figure 2).

The univariate analysis showed that metastasis at diagnosis was significantly associated with mortality (Table 2). In the multivariate analysis, the risk factor significantly associated with mortality was the presence of metastasis at diagnosis, while first-line immunotherapy demonstrated a protective role (Table 4).

Histopathologic and Molecular Data

Mucosal melanomas can occur in all sites where mucosal melanocytes are present. While perianal, genital, and perioral skin normally harbors melanocytes (and, consequently, these are sites of origin of benign and malignant melanocytic tumors, albeit rare), melanocytes are usually absent in the bladder mucosa. In the rare case of bladder melanoma, a spread of melanocytes from the urethra could explain its etiopathogenesis. In the nasal and paranasal cavities, melanocytes can be found both in the epithelium and in the stroma, mainly in the dark-skinned population.

Delayed site-related detection of these melanomas can explain their architecture, which is often nodular or polypoid, and, at the same time, their thickness, which is usually higher than most cutaneous melanomas.

Most mucosal melanomas are often associated with an in situ lateral spread on the mucosal surface (Figure 3), which is a supportive feature that the tumor is primitive. Cytologically, mucosal melanomas are remarkably variable; neoplastic cells can be spindle, rhabdoid, epithelioid, small, or giant pleomorphic (often multinucleated), thus causing challenging diagnostic problems in differentiating them from lymphomas, carcinomas or sarcomas. Necrotic areas are frequent and mitotic activity is usually high (Figure 4). Due to their heterogeneous appearance, immunohistochemical staining (S100, MART-1, HMB45 or SOX10) is often required to demonstrate the melanocytic origin of the neoplasm.

In our series, epithelioid features were prevalent (25 out of 33 cases). Two cases were composed of spindle hyperpigmented cells, two cases had a lymphocytic-like appearance, one was rhabdoid and, in three cases, the cytological pattern of growth was mixed (Figure 5).

Mean Breslow thickness in mucosal melanoma was 6.7 with no appreciable difference between different anatomical sites; no Breslow thickness was reported in sinonasal melanomas due to the sparse and fragmented nature of biopsy specimens. Tumor ulceration was noted in 11 samples. In one case of vulvar melanoma, a residual melanocytic nevus was found at the periphery of the tumor.

No samples undergoing biomolecular analysis had BRAF or NRAS mutation, while 3 cases had c-KIT and 3 cases KRAS mutations.

![Figure 2. Kaplan Meier estimates for overall survival. (A) OS in mucosal melanomas. (B) Stratification of the cohort by the site of the primary tumor.](image-url)
### Table 3. Univariable model of risk factors for mortality in mucosal melanomas.

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.02 (0.97-1.07)</td>
<td>0.292</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.93 (0.67-5.45)</td>
<td>0.216</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinonasal</td>
<td>1.90 (0.57-6.29)</td>
<td>0.291</td>
</tr>
<tr>
<td>Urogenital</td>
<td>0.25 (0.05-1.09)</td>
<td>0.066</td>
</tr>
<tr>
<td>Metastasis at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.75 (1.79-42.76)</td>
<td>0.007</td>
</tr>
<tr>
<td>Site of metastasis at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin/regional lymph node</td>
<td>ref.</td>
<td></td>
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<tr>
<td>Visceral</td>
<td>3.30 (0.34-31.96)</td>
<td>0.302</td>
</tr>
<tr>
<td>Cerebral</td>
<td>6.21 (0.53-72.00)</td>
<td>0.144</td>
</tr>
<tr>
<td>≥2 sites</td>
<td>2.50 (0.22-27.95)</td>
<td>0.456</td>
</tr>
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<td>Surgery</td>
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</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Debulking</td>
<td>0.19 (0.02-1.59)</td>
<td>0.129</td>
</tr>
<tr>
<td>Radical</td>
<td>0.33 (0.09-1.16)</td>
<td>0.085</td>
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<tr>
<td>First-line biological therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>0.88 (0.26-2.95)</td>
<td>0.840</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>1.16 (0.13-9.63)</td>
<td>0.890</td>
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<tr>
<td>Imatinib</td>
<td>2.71 (0.31-23.21)</td>
<td>0.362</td>
</tr>
<tr>
<td>First-line chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.84 (0.23-14.66)</td>
<td>0.561</td>
</tr>
<tr>
<td>Second-line systemic therapy</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>0.71 (0.09-5.68)</td>
<td>0.752</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>1.42 (0.17-11.30)</td>
<td>0.740</td>
</tr>
<tr>
<td>Cytoreductive-palliative radiation therapy</td>
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</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.65 (0.56-4.90)</td>
<td>0.360</td>
</tr>
</tbody>
</table>

HR: hazard ratio  
CI: confidence interval

Detailed descriptive data from histopathologic and molecular data are reported in Table 5.

**Discussion**

This 11-year retrospective study shows that mucosal melanoma is a tumor typically arising in the older population, with a median age of 82, not significantly influenced by site of origin [13]. Demographic data also confirm that mucosal melanoma has a higher prevalence in females [9]; this result is largely driven by cases of vulvovaginal melanoma in the urogenital melanoma subgroup. Surprisingly, we have no records of oral cavity mucosal melanomas, which alone have been described as the second most frequent location in the head and neck region [2,8,9].

Histologically, most cases were made by epithelioid cells, regardless of the site of origin. In many cases, pleomorphic
**Table 4. Multivariable model of risk factors for mortality in mucosal melanomas.**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.02</td>
<td>(0.96-1.09)</td>
<td>0.574</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.33</td>
<td>(0.98-11.25)</td>
<td>0.107</td>
</tr>
<tr>
<td>Metastasis at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26.55</td>
<td>(3.18-221.42)</td>
<td>0.001</td>
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<tr>
<td>First-line biological therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>0.10</td>
<td>(0.01-0.75)</td>
<td>0.025</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>0.04</td>
<td>(0.01-0.91)</td>
<td>0.044</td>
</tr>
<tr>
<td>Imatinib</td>
<td>0.09</td>
<td>(0.0-2.02)</td>
<td>0.133</td>
</tr>
</tbody>
</table>

CI: confidence interval

**Figure 3.** Vulvar melanoma (A) Clinical overview of a nodular hyperpigmented lesion of the vulva. (B) Dermoscopy of the nodular part shows a blue-black structureless area with shiny white structures and negative pigment network at the implant base. (C) Dermoscopy of the flat part shows blue and black globules and blotches, a blue-white veil, and shiny white structures. (D) Histology: the neoplasm is largely ulcerated, shows discrete necrotic areas, and reaches 11 mm thickness according to Breslow. At a higher power view, vascular invasion of neoplastic cells is visible (arrow).
areas with bizarre, giant cells were present. Only two cases of spindle cell melanomas were recorded, even if spindle cell areas occurred in three cases with a mixed pattern of growth. The epithelioid features and the presence of melanin, which in rare cases can be massive, simplified the diagnosis; vice versa, differential diagnosis resulted challenging in two cases of lymphoma-like melanoma (one anorectal and one genital) and an immunohistochemical panel of stains was necessary to rule out a lymphoproliferative process.

More than half of mucosal melanomas (54.4%) manifested with metastasis at diagnosis. Patients who were discovered with metastasis have an increased HR for death as highlighted by univariate analysis (Table 3); in addition, the prognostic value of metastatic status at diagnosis was reported by the multivariate model. These findings corroborate the evidence that diagnosing advanced-stage tumors has a relevant influence on prognosis [14]. As previously discussed [9], the site of origin of neoplasia, mostly anatomically occult, is a relevant cause of late diagnosis. Incidence of mucosal melanomas in older age could be an additional cause, as older people can delay seeking physician consultation.

The multivariate model also showed that the administration of immunotherapy as a first-line treatment was a protective factor for death, with a statistical significance both for nivolumab and pembrolizumab. No significance has been obtained for imatinib, because of the small sample.

It is interesting to highlight that, despite the small sample size in the current study, our data support the utility of
also reported [18,19] that females diagnosed with mucosal melanomas have higher survival, unrelated to the site of origin; thus, the longer survival in this cohort could also be driven by the prevalence of vulvovaginal melanoma in the subgroup. Surgical treatment with radical intent, undergone by all patients with urogenital melanoma in our series, may be an additional factor influencing longer survival.

No case of male urogenital melanomas was reported in the database of the Pathology Unit of our hospital confirming that mucosal melanoma of the male genital tract is a very rare occurrence [4].

Urogenital Melanoma

In our series, urogenital melanoma showed 4 cases of metastasis in locoregional lymph nodes and no distant metastasis at diagnosis. Moreover, urogenital melanoma is the subgroup with the longer OS, with full survival at 24 months and decreased survival only after 26 months (Figure 2). The absence at diagnosis of disseminated disease is probably the most relevant factor that influences cohort survival. It was also reported [18,19] that females diagnosed with mucosal melanomas have higher survival, unrelated to the site of origin; thus, the longer survival in this cohort could also be driven by the prevalence of vulvovaginal melanoma in the subgroup. Surgical treatment with radical intent, undergone by all patients with urogenital melanoma in our series, may be an additional factor influencing longer survival.

No case of male urogenital melanomas was reported in the database of the Pathology Unit of our hospital confirming that mucosal melanoma of the male genital tract is a very rare occurrence [4].

Urogenital melanomas in our database manifested as a vegetating mass, new pigmentation of the external genitalia, or urogenital bleeding (Table 2).

Anorectal Melanoma

Patients with anorectal melanoma showed a younger age at diagnosis (Table 1).
Additional evidence emerging from Kaplan-Meier analysis is that the mortality of sinonasal mucosal melanomas was higher in the first 24 months and then decreased, reaching a plateau (Figure 2). Factors that may influence this behavior, such as radiation therapy, administered to all cohort patients, are still unclear and need to be further analyzed in a larger sample.

Sinonasal melanomas in our series manifested with epistaxis, nasal obstruction, and one case of eyelid ptosis (Table 2).

**Table 5. Mucosal melanoma pathological data and stratification by the site of origin.**

<table>
<thead>
<tr>
<th></th>
<th>Mucosal melanomas (n=33, 100%)</th>
<th>Sinunasal (n=9, 27.3%)</th>
<th>Anorectal (n=13, 39.4%)</th>
<th>Urogenital (n=11, 33.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow, n, mean ± SD (range)</td>
<td>10, 6.7 ±5.2 (0.6-17)</td>
<td>-</td>
<td>3, 7.1 ±5.3 (1.4-12)</td>
<td>7, 6.5 ±5.6 (0.6-17)</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>0</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>11 (33.3)</td>
<td>0 (0.0)</td>
<td>5 (38.5)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid cells</td>
<td>25 (75.7)</td>
<td>9 (100)</td>
<td>10 (76.9)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Spindle cells</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
<td>1 (7.6)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Small cells</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
<td>1 (7.6)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Rhabdoid cells</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
<td>1 (7.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (9.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (27.2)</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (21.2)</td>
<td>1 (11.1)</td>
<td>1 (7.7)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (15.2)</td>
<td>1 (11.1)</td>
<td>2 (15.4)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>BRAF, wt</td>
<td>25 (75.8)</td>
<td>8 (88.9)</td>
<td>10 (76.9)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>c-KIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V560D</td>
<td>3 (9.1)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>wt</td>
<td>8 (24.2)</td>
<td>2 (22.2)</td>
<td>5 (38.5)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>NRAS, wt</td>
<td>9 (27.3)</td>
<td>3 (33.3)</td>
<td>4 (30.8)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>KRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.A146V</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>p.G12A</td>
<td>1 (3.0)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>p.G12C</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>wt</td>
<td>1 (3.0)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

LVI: lymphovascular invasion

Even though all patients surgically managed in this subgroup underwent a radical intent procedure, Kaplan-Meier analysis showed the worst survival. This result is consistent with previous reports [15,18]. It is reasonable to suppose that a more widespread metastatic disease at diagnosis in this subgroup is the reason for this difference (Table 1). It was demonstrated that anorectal melanoma has an intrinsically aggressive behavior because of the high propensity to develop distant and brain metastases [18]; in our series, this subgroup is the only one manifesting with 2 cases of cerebral metastasis and with 3 cases of multiple visceral metastases at diagnosis.

Anorectal melanomas diagnosed in our clinics had presenting symptoms such as rectal bleeding, anemia, and prolapse of the tumor mass (Table 2).

**Sinonasal Melanoma**

In the sinonasal region, Breslow thickness is not easy to apply because of biopsy sampling. In fact, all surgical treatments proposed to this cohort of patients were debulking procedures that usually prevent obtaining a well-oriented full-thickness specimen for histopathological analysis.

Conclusions

In conclusion, different strategies have to be developed to avoid late diagnosis; so far, there are no targeting campaigns or specific advice that can help physicians from different specialties (i.e. gynecologists) to get early diagnoses of this rare melanoma subsets. As promising results, the use of immunotherapy might impact the natural history of mucosal melanomas in improving overall or disease-free survival.


Lipoid proteinosis, also known as Urbach-Wiethe disease, is a rare autosomal recessive condition, characterized by a mutation of extracellular matrix protein 1 (ECM1), leading to deposition of collagenous material in the skin and tissues [1]. This disease may be associated with diabetes and other abnormalities. We report a case of lipoid proteinosis associated with celiac disease in a 23-year-old man.

A 23-year-old patient was admitted to our department for facial edema evolving for 1 year, with no other associated signs. The dermatological examination revealed an infiltrated edema of the face, predominantly on the forehead, associated with discrete 3 mm yellow papules in the ear pavilion (figure 1), without mucosal involvement. The histological study of the papule showed a homogeneous, eosinophilic, PAS-stained dermal deposit of hyaline substance, in favor of lipoid proteinosis. Laboratory tests revealed hypochromic microcytic anemia (hemoglobin of 9 g/dl), ferritin 7 ng/ml, hypcholesterolemia 0.7 mmol/l with normal albumin and protein. The patient was further evaluated with an upper endoscopy. The histological examination of the duodenal biopsy revealed atrophic pangastritis with villous atrophy. Test IgA anti-transglutaminases were highly positive at low titer. The diagnosis of celiac disease was established. The workup for other disease locations of lipoid proteinosis was negative. The therapeutic approach was to put the patient on a gluten-free diet and acitretin for his skin lesions. After 3 months of treatment with acitretin, the dermatological examination noted a minor improvement of the edema. The cutaneous lesions were still present, without new lesions. Then, he was lost to follow-up.

Lipoid proteinosis, also called hyalinosis cutis mucosae, is a rare, non-life-threatening condition and was first described in 1929 by a dermatologist and an otorhinolaryngologist, E. Urbach and C. Weithe [2]. Around 300 cases have been reported in the literature with higher prevalence in South Africa and Sweden. Hoarseness of the voice is usually the first sign of this disease that appears in childhood. The dermatological manifestations include vesiculobullous lesions, hyperkeratotic plaques on the extensor surfaces of elbows, knees, and hands, yellow papules, and multiple acneiform and pox-like scars that are seen on the face [3]. Moniliform blepharitis is the
characteristic ocular involvement, affecting the eyelid margins. This disease may affect all organ systems of the body.

Histologic features consist of thick homogeneous, eosinophilic hyaline material, periodic acid-Schiff positive, in the basement membrane and the dermis [4].

Some cases in the literature have mentioned the association of lipoid proteinosis with diabetes [5], and with epilepsy [6]. This is the first report describing an association with coeliac disease.

Currently, there is no effective treatment. Several molecules have been used with different results, such as D-penicillamine, dimethyl-sulfoxide, and retinoids for their inhibitory effect on collagen. Also, CO2 laser, dermabrasion, and chemical peeling represent other therapeutic means for the management of cutaneous lesions [3].

Knowledge of this rare disease will aid health professionals in diagnosing it early, and in providing the appropriate treatment to improve the quality of life.

References

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Figure 1. Yellowish-white papules of the ear.
Dermoscopy of Infectious Dermatoses: is it Time to Replace the Terms “Entodermoscopy” and “Entomodermoscopy” with “Infectiouscopy”?

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Citation: Errichetti E. Dermoscopy of infectious dermatoses: is it time to replace the terms “entodermoscopy” and “entomodermoscopy” with “infectiouscopy”? Dermatol Pract Concept. 2023;13(1):e2023021. DOI: https://doi.org/10.5826/dpc.1301a21

Accepted: April 13, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

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Besides the classical use in the oncological setting, dermoscopy has showed to be helpful to assist the recognition of several non-neoplastic dermatoses (general dermatology), including inflammatory and infectious conditions [1]. The initial applications in this regard date back to 1997 and concerned parasitic infections (scabies and larva migrans), afterwards several papers on the use of dermoscopy in the field of general dermatology have progressively published, with 305 dermatoses (including relevant disease variants typified by dermoscopic peculiarities) showing at least a dermoscopic description at the end of 2020 [2].

Over the time, the terms “inflammoscopy” and “entodermoscopy” (or “entomodermoscopy”) have gradually spread in the scientific community to refer to dermoscopy of inflammatory and infectious diseases, respectively, as their roots link the fields of inflammatory diseases and entomology with dermoscopy [3-4]. However, while the former denomination is still appropriate, there is a need to update the latter. In fact, the terms “entodermoscopy”/“entomodermoscopy” were initially conceived to refer to the study of parasitic dermatoses (including arthropod bites and stings) [3-4] based on the etymology of the word “entomology” (from Ancient Greek ἔντομον (entomon) “insect”, and -λογία (-logia) “study of”), [5] yet nowadays the use of dermoscopic assessment has expanded to many non-parasitic infections [2]. In detail, according to a literature overview about the applications of dermoscopy in general dermatology updated to the end of 2020, a total of 25 parasitoses and arthropod bites/stings turned out to have at least one dermoscopic description, which was remarkably lower than the sum of non-parasitic infections (51, with 11, 21, 19 being viral, bacterial and fungal, respectively) (a complete list is reported in Table 1) [2]. Interestingly, whereas the review showed only a little increase in the publication trend about parasitoses over recent times, it displayed a significant leap of articles dealing with dermoscopy of non-parasitic infections in the last few years (36 vs 9 addressing parasitoses in the time span between 2016 and 2020 – Table 1), thus making this topic a promising research field in the coming future [2].

Based on the foregoing, when talking about dermoscopy of infectious dermatoses, it would be reasonable to think to replace the terms “entodermoscopy” and “entomodermoscopy”, which include a limited part of the infectious spectrum of skin diseases, with “infectiouscopy”, that is an “umbrella” term as its root refers to all infectious dermatoses.
Table 1. List of both parasitic and non-parasitic infections whose dermoscopic findings have been described in the literature.

<table>
<thead>
<tr>
<th>Parasitic dermatoses* (year of first description)</th>
<th>Non-parasitic infections (year of first description)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=25</strong></td>
<td><strong>N=51</strong></td>
</tr>
<tr>
<td>• Scabies (1997)</td>
<td>• Tinea nigra (2001)</td>
</tr>
<tr>
<td>• Cutaneous larva migrans (1997)</td>
<td>• Tinea corporis (2004)</td>
</tr>
<tr>
<td>• Cutaneous leishmaniasis (2009)</td>
<td>• Genital warts (2008)</td>
</tr>
<tr>
<td>• Phthiriasis (2009)</td>
<td>• Verruca vulgaris (2008)</td>
</tr>
<tr>
<td>• Bullous scabies (2010)</td>
<td>• Plantar warts (2009)</td>
</tr>
<tr>
<td>• Crusted scabies (2010)</td>
<td>• Lupus vulgaris (2009)</td>
</tr>
<tr>
<td>• Demodicosis (2010)</td>
<td>• Pitted keratolysis (2010)</td>
</tr>
<tr>
<td>• Tick bite (2010)</td>
<td>• Trichobacteriosis axillaris (2012)</td>
</tr>
<tr>
<td>• Trombiculiasis (2014)</td>
<td>• Mycetoma (2014)</td>
</tr>
<tr>
<td>• Wasp (hymenoptera, vespidae) stings (2014)</td>
<td>• Cutaneous blastomycosis (2015)</td>
</tr>
<tr>
<td>• Pediculosis corporis (2014)</td>
<td>• Pityriasis versicolor (2015)</td>
</tr>
<tr>
<td>• Germanysus gallinae mite cutaneous infestation (2015)</td>
<td>• Achromic pityriasis versicolor (2016)</td>
</tr>
<tr>
<td>• Thaumetopoea pityocampa cutaneous reactions (2016)</td>
<td>• Condylomata lata (2016)</td>
</tr>
<tr>
<td>• Bed bug (Cimex lectularius) bites (2016)</td>
<td>• Tinea manuum (2016)</td>
</tr>
<tr>
<td>• Acute cutaneous leishmaniasis (2017)</td>
<td>• Tinea of vellus hair (2016)</td>
</tr>
<tr>
<td>• Wound myiasis (2017)</td>
<td>• White Piedra (2016)</td>
</tr>
<tr>
<td>• Disseminated strongyloidiasis (2018)</td>
<td>• Pseudomonas folliculitis (2016)</td>
</tr>
<tr>
<td>• Cutaneous loxoscelism (2018)</td>
<td>• Contagious eczema (ORF) (2016)</td>
</tr>
<tr>
<td>• Post-kala-azar dermal leishmaniasis (2018)</td>
<td>• Tinea incognito (2016)</td>
</tr>
<tr>
<td>• Cydnidae pigmentation (2019)</td>
<td>• Staphylococcal scalded skin syndrome (2016)</td>
</tr>
<tr>
<td>• Infectious folliculitis (parasitic) (2019)</td>
<td>• Disseminated cryptococcosis with cutaneous involvement (2017)</td>
</tr>
<tr>
<td></td>
<td>• Chromoblastomycosis (2017)</td>
</tr>
<tr>
<td></td>
<td>• Peruvian wart (2017)</td>
</tr>
<tr>
<td></td>
<td>• Milker’s nodule (2017)</td>
</tr>
<tr>
<td></td>
<td>• Borderline tuberculoid leprosy (2017)</td>
</tr>
<tr>
<td></td>
<td>• Syphilis (palmar syphiloderm) (2017)</td>
</tr>
<tr>
<td></td>
<td>• Histoid leprosy (2017)</td>
</tr>
<tr>
<td></td>
<td>• Pityrosporum folliculitis (2018)</td>
</tr>
<tr>
<td></td>
<td>• Sporotrichosis (2018)</td>
</tr>
<tr>
<td></td>
<td>• Tinea manuum (2018)</td>
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<td>• Candidal balanitis (2018)</td>
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<td></td>
<td>• Mycobacterium marinum skin infection (2019)</td>
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<td>• Majocchi’s granuloma (2019)</td>
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<td></td>
<td>• Infectious folliculitis (fungal) (2019)</td>
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<td>• Infectious folliculitis (viral) (2019)</td>
</tr>
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<td></td>
<td>• Infectious folliculitis (bacterial) (2019)</td>
</tr>
<tr>
<td></td>
<td>• Talaromyces (Penicillium) marneffei infection</td>
</tr>
<tr>
<td></td>
<td>• Tuberculoid leprosy (2019)</td>
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</tr>
<tr>
<td></td>
<td>• Lepromatous leprosy (2019)</td>
</tr>
<tr>
<td></td>
<td>• Type 1 lepra reaction (2019)</td>
</tr>
<tr>
<td></td>
<td>• Type 2 lepra reaction (2019)</td>
</tr>
<tr>
<td></td>
<td>• Tuberculosis verrucosa cutis (2020)</td>
</tr>
<tr>
<td></td>
<td>• Lichen scrofulosorum (2020)</td>
</tr>
<tr>
<td></td>
<td>• Focal epithelial hyperplasia (2020)</td>
</tr>
<tr>
<td></td>
<td>• Chilblain-COVID-19-like skin lesions (2020)</td>
</tr>
<tr>
<td></td>
<td>• Syphilis (penile annular syphiloderm) (2020)</td>
</tr>
</tbody>
</table>

*Including arthropod bites and stings
References

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Bullous pemphigoid (BP) affects predominantly elderly patients, and the disease incidence rises exponentially with age. A high prevalence of diabetes mellitus (DM) in patients with BP has been noticed, ranging from 20 to 30% [1].

The treatment of BP patients is challenging and should be carefully assessed bearing in mind their multiple comorbidities. Corticosteroids are the mainstay of treatment for BP. However, their systemic use is limited in diabetic patients by the risk of acute hyperglycemic complications. This is particularly concerning given the age group of BP patients and the chronicity of treatment. Adjunctive therapy with immunosuppressants such as azathioprine, mycophenolate mofetil or methotrexate may also be needed [2]. Also, novel targeted therapeutic approaches such as omalizumab and dupilumab have been reported as effective alternatives, but their use in BP is still off-label [3].

Several population-based studies supported an increased risk of developing BP in diabetic patients treated with dipeptidyl peptidase-4 inhibitors (DPP4i). A recent meta-analysis showed that the odds ratio (OR) for BP among patients receiving any DPP4i ranged from 1.27 to 3.45 [4]. The exact pathogenesis of how DPP4i might induce BP remains largely unclear and it is not known if the suspension of DPP4i can revert this immunological process. However, the clinical outcome appears to be better if DPP4i is discontinued.

A presumed association between BP and glucagon-like peptide-1 (GLP-1) receptor agonists has also been reported [5]. The underlying mechanism is unclear, however since DPP4i and GLP-1 receptor agonists both rely on enhancing the activity of the incretin hormone GLP-1, a common effect between these two classes of antidiabetic drugs should be sought. Although more robust studies are required, we suggest that this association is taken into account when selecting the most appropriate medication for BP patients.

Other widely used antidiabetic drugs like second-generation sulfonylureas and metformin seem safer options, but their use can be limited by the patient’s comorbidities [6]. The sodium–glucose cotransporter (SGLT2) inhibitors also seem like good alternatives. These drugs do not increase the risk of hypoglycemia, have low rates of adverse effects and may be continued in patients with moderate renal impairment. Overall, they can be used in selected BP patients.
In many cases, insulin is the most suitable choice, particularly for inpatients on corticosteroids. Morning basal insulin may closely fit the glucose excursion induced by a single dose of morning corticosteroid. The initial dose and titration should take into account the patient's weight and dose of corticosteroid. Dairy adjustments are frequently necessary and often difficult to predict.

Based on the previous data, a treatment algorithm for BP patients with type 2 DM is proposed in Fig. 1.

In conclusion, it is decisive that we view BP patients beyond a single-disease framework and treat them in the context of multi-morbidities. Diabetes management in these patients can be particularly troublesome and, to date, there are no orienting guidelines on this matter. Endocrinologists should be aware of BP as a challenging problem in patients with DM and collaboration with dermatologists is essential for good outcomes.

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A Review of the Impact of Sun Safety Interventions in Children

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Key words: behavioral change, skin cancer, sunscreen, sun protection, UV radiation


Accepted: November 3, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: In the United States, melanoma and non-melanoma skin cancers comprise the largest proportion of new cancer diagnoses every year. The prevalence of skin cancer can be largely reduced if proper preventative behaviors are adopted at an early age.

Objectives: We assessed the impact of various informational, economic, and environmental interventions on sun-protective behaviors, knowledge, attitudes, and sun exposure in the pediatric population reported in previous studies.

Methods: A systematic search for relevant articles was conducted using three databases. Studies were included if they met the following three criteria: study subjects less than 18 years old, clear, measurable interventions and outcomes, and publication in the English language.

Results: A total of 66 studies were included, of which 48 resulted in positive behavioral changes (i.e. increases in sunscreen application, use of hats and sun-protective clothing, shade-seeking, and avoidance of outdoor activities during peak UV radiation), 28 resulted in increased knowledge, 2 resulted in changes in attitudes towards tanning, and 10 resulted in decreased sun exposure effects (i.e. new sunburns, number of new nevi, and change in pigmentation of the skin).

Conclusions: It is crucial that children be educated on the importance and benefits of sun protection. Although a variety of interventions showed promise in achieving this goal, the challenges associated with adopting change were evident. This review provides direction for future interventions aimed at improving sun safety in children and illustrates the potential impact that early intervention can have on the incidence of skin cancer in future generations.
Introduction

In the United States, skin cancer is the most common malignancy and is estimated to affect one in five individuals in their lifetime [1]. The overall incidence of melanoma and non-melanoma skin cancers (NSMC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), has been increasing rapidly in recent decades. Melanoma is the most lethal type of skin cancer, and it is predicted that over 7,500 Americans will die from melanoma in 2022 [2]. Although NMSCs typically carry a more favorable prognosis, they place a large burden on the United States healthcare system, with an estimated annual cost of $4.8 billion [3]. The largest preventable risk factor for both melanoma and NMSC is ultraviolet radiation (UVR) exposure [4]. UVR is a risk factor for skin cancer at any age; however, children are at an increased risk of excessive UVR exposure [5]. Children spend a significant portion of their time outdoors at school when the UV index is highest, where activities such as recess and sporting events can result in extended periods of UVR exposure. In fact, sun damage is cumulative, and about 23 percent of a person’s lifetime sun exposure happens by the age of 18 [6]. There is a strong relationship between total sun exposure and non-melanoma skin cancers, and there is a clear relationship between sunburns and the development of melanoma [7].

Interventions aimed at preventing excessive exposure to harmful UVR can decrease the incidence of skin cancer. The American Cancer Society provides several recommendations aimed at primary prevention of skin cancer: 1) seek shade when UV radiation is strongest (10:00 A.M. - 4:00 P.M.); 2) wear sun-protective clothing (i.e. long sleeved shirts and pants); 3) wear wide-brimmed hats; 4) apply sunscreen with a minimal SPF of 30; and 5) avoid tanning beds [8]. In addition to primary prevention methods, secondary prevention methods include regular skin self-examinations and professional skin examinations. Applying both prevention techniques has illustrated a decrease in the incidence, morbidity, and mortality of skin cancer [4].

Since childhood sun exposure increases the risk of skin cancer, it is essential to educate children about primary prevention measures as well as take action to promote sun-protective behaviors. In this review, we evaluated studies that aimed to either educate or change the behavior of children regarding sun safety. By doing this, we aimed to identify the techniques used and summarize them as an example for much-needed future educational efforts.

Methods

The following criteria were used to identify eligible studies: 1) study subjects must be less than 18 years old; 2) study must have clear interventions and outcomes (e.g. behavior or knowledge); and 3) study must be published in the English language.


Results

The initial literature search of Ovid Medline, Ovid Embase, and Scopus yielded 143 articles. After the articles were reviewed and duplicates excluded, 66 articles met the inclusion criteria [9-74].

Types of Interventions:

Most studies had an intervention that delivered sun-protective educational information to the study population (Figure 1). Of the 62 studies that focused on providing information, some of the most popular methods included giving a presentation, handing out newsletters or flyers, and implementing sun safety lessons in the school curriculum. In addition, 17 studies relied on economic intervention. From these studies, distribution of free sunscreen to children was the most popular provision. Other economic interventions included providing protective clothing, hats, and sunglasses. Lastly, 3 studies changed the physical environment by adding resources such as shaded structures for children to use during peak UV light hours (Figure 2).

Knowledge as an Outcome:

There were 32 studies that measured change in knowledge as an outcome after implementation of the intervention. Of those 32 studies, 27 assessed only for the child’s knowledge, 4 assessed only for the parents’ knowledge, and 1 assessed for both the child and parents’ knowledge. Of the studies that focused only on measuring the change in the children’s knowledge after intervention, twenty-six studies noted a significant increase in baseline knowledge and only one study revealed nonsignificant changes. Winnett et al. illustrated that even after intervention, the children still had minimal knowledge of appropriate sunscreen use and frequency [67]. Even though Hingle et al. showed a statistically significant overall increase in knowledge, it was primarily driven by knowledge about skin cancer types [27]. The rest of the knowledge-based questions related to UV radiation, precautions to take to avoid sunburn, and suntanning showed no significant changes. Of the four studies directed at only
**TYPES OF INTERVENTION**

- **EDUCATIONAL**: 62 studies, 75%
- **ECONOMIC**: 17 studies, 21%
- **ENVIRONMENTAL**: 3 studies, 4%

Figure 1. A pie chart illustrating the various methods of intervention used from all 62 studies.

**SUCCESSFUL STUDIES BY TYPE OF OUTCOME MEASURED**

- **BEHAVIOR**: 50 studies
- **KNOWLEDGE**: 50 studies
- **SUN EXPOSURE**: 10 studies
- **ATTITUDES**: 5 studies

Figure 2. A bar chart comparing studies that were successful in improving the measured outcome to studies that were not successful in improving the measured outcome.
measuring the change in parents’ knowledge, two of them did not result in an increase in the parents’ knowledge. Glanz et al. used questions to create a knowledge index that was measured for the parents [14]. The knowledge index was relatively high at baseline and remained virtually unchanged in both intervention groups. Glanz et al. assessed the knowledge of parents and staff [53]. Although their knowledge scores were relatively high to begin with, they improved slightly; however, neither of the changes was statistically significant. In the study that tested both the children’s and parents’ knowledge, parents were reported to have decreased in knowledge, while elementary and middle schoolers had increased and high schoolers had no change [62].

Attitudes Toward Tanning as an Outcome:
Five studies assessed children’s attitudes and perceptions of tanning before and after intervention. Three of the five interventions were considered failures. Kristjánsson et al. developed an educational tool kit about skin cancer prevention [74]. This tool kit included a manual for teachers, animated comic figures, a 7-minute video, and recommendations on how to behave in the sun. The students’ attitude to refrain from tanning was not significantly changed. Regarding mid-day sun avoidance, most students only progressed from a pre-contemplation stage to a contemplation stage. Kouzes et al. utilized a sun safety curriculum which included teachers adopting sun safety into their lessons, UV index announcements on the speaker, and guest presenters on UV and sun safety [62]. Although elementary students and middle school students had improved perceptions, high school students maintained a positive attitude towards tanned skin. Buller et al. utilized an educational computer program on sun safety based on the “Sunny Days, Healthy Ways” sun safety curriculum [33]. This CD-ROM program did not improve attitudes toward sun-protective behavior. Barankin et al. enhanced an existing “Sun and the Skin” program by educating the parents about the program, providing supplemental information, and distributing sunscreen [28]. The students in the enhanced group illustrated improvement over the control and standard groups in their attitude towards tanning. David et al. included an educational presentation and interactive activities delivered by university students, who underwent rigorous training and volunteering as part of their undergraduate and graduate-level courses [32]. After the intervention, participants reported less appeal for tanned skin than before the intervention (p<0.001).

Behaviors as an Outcome:
There were 60 studies that measured change in sun-protective behaviors as an outcome after implementation of the intervention. Of those 60 studies, 48 had interventions that were successful at impacting at least one behavior relating to sun protection in either the children or their parents (Figure 3).

![Percent Failure by Intervention Type for Behavioral Outcomes](image-url)

**Figure 3.** A bar chart illustrating what percentage of studies were unsuccessful in changing behavior based on the type of intervention.
A few commonly studied behaviors include frequency of sunscreen application, use of hats and sun-protective clothing, shade-seeking, and avoidance of outdoor activities during peak UV radiation. For example, Crane et al. is a randomized controlled trial that found changes in many behaviorial outcomes after sending newsletters on sun protection and skin cancer to parents and their children over the course of three years [38]. Specifically, the post-intervention group demonstrated increased use of sunscreen, protective clothing, hats, shade-seeking, and midday sun avoidance compared to baseline; however, a statistically significant difference compared to the control group was only present for a few select behaviors and in certain years. Conversely, Bauer et al. is a randomized controlled trial in which parents were randomized to receive either educational material on sun protection, free sunscreen, or neither, and the results demonstrated no significant differences between the groups in sun-protective behaviors or the development of melanocytic nevi in the children [36].

Sun Exposure as an Outcome:
There were 15 studies that measured sun exposure via physical skin changes as an outcome after implementation of the intervention. A few commonly studied metrics include incidence of new sunburns, number of new nevi, and change in pigmentation of the skin. Of the 10 studies that measured incidence of sunburn as an outcome, 8 studies showed fewer sunburns as a result of the intervention, whereas one study showed no effect on sunburns and another study showed an increase in the number of sunburns despite the intervention [61]. Of the 6 studies that looked at increased pigmentation (i.e., tanning, melanin) as an outcome, only 2 studies demonstrated that their intervention decreased the level of skin pigmentation. Of the 3 studies that looked at development of new melanocytic nevi as an outcome, none of them showed a statistically significant difference in the development of new nevi post-intervention.

Discussion
The goal of this review was to evaluate the impact of various informational, economic, and environmental interventions on sun-protective behaviors, knowledge, attitudes, and sun exposure in the pediatric population. Targeting children is important because, theoretically, the earlier that sun-protective habits are formed, the earlier primary prevention methods from dangerous UV rays can be implemented and lower the burden of future skin cancer. As many of the techniques reviewed were successful in instilling knowledge and sun safety practices, this discussion highlights the interventions that failed to alter children's behaviors, knowledge, attitudes, and sun exposure. Using this information, future studies directed at the pediatric population can alter their interventions to be better suited to have a significant impact on these outcomes.

Children’s knowledge about skin cancer and the importance of sun protection was improved in all but two studies [62, 67]. Kouzes et al. implemented a sun safety curriculum which included teachers incorporating sun safety into their lessons, UV index announcements on the speaker, and guest presenters on UV and sun safety [62]. The curriculums used differed based on grade level (preschool through first grade used CATCH Global Foundation’s Ray and the Sunbeatables, grades kindergarten through eighth grade used the Environmental Protection Agency SunWise, and grades six through twelve used SunSmart U developed by the Skin Cancer Foundation). Knowledge was improved in elementary and middle schoolers; however, high schoolers did not have any change in knowledge of sun protection strategies. Knowledge deficits in older age groups could be attributed to inadequate use of the curriculum and could suggest that additional support may be needed from a statewide non-profit organization dedicated to cancer control. Skonieczna et al. demonstrated the significance of partnerships within schools to create long-lasting sun safety programs, so such support could encourage increased participation [75]. Winnen et al. studied the effects of an intervention that included informational posters in prominent locations, a poster providing feedback about how many people are practicing the SafeSun program, a weekly lottery ticket for people wearing sun-protective clothing, and lifeguards modeling the SafeSun logo on their clothing [67]. Knowledge about skin cancer, its causes, and how to appropriately use sunscreen remained low. This intervention did not include formal information lessons, which could explain the lack of knowledge related to skin protection.

Several studies demonstrated positive attitudes towards tanned skin even after an intervention was implemented [33, 62, 74]. In the previously mentioned study by Kouzes et al., in addition to not showing improvements in knowledge, high schoolers also continued to value the appearance of tanned skin [62]. Despite acknowledging the risks associated with tanned skin, high school students still maintained a positive attitude towards tanned skin. This illustrates that because older children perceive tanned skin as desirable, they are willing to risk their health to fit into societal norms [76]. Another study provided a manual for teachers, animated comic figures, a 7-minute video, and recommendations on how to behave in the sun to adolescents [74]. The students’ attitudes to refrain from tanning were not significantly changed. Previous studies have shown that when children reach adolescence, their appreciation of suntans increases [7, 77]. Therefore, it might be beneficial to start motivating attitude changes to sunbathing before adolescence. Lastly,
Buller et al. used a CD-ROM educational computer program based on a sun safety education program and also failed to improve children’s attitudes towards sun protective behaviors [33]. Changing attitudes about suntanning is a challenging task in this population. Branstom et al. surveyed 2615 adolescents and uncovered that the most frequent motive for sunbathing was that it made them feel more attractive [76]. Media influence plays a large role in affecting the desire to tan by promoting the idea that tan skin equates to looking healthy and attractive [78]. Changing the attitudes of children towards tanning and their motivation to intentionally tan will remain challenging as long as societal pressure and media influence promote tanned skin.

Many studies were able to demonstrate a positive effect on sun-protective behaviors; however, there were some that were unsuccessful. A common theme among several of the unsuccessful studies was the utilization of interventions that involved brief (30-60 minute), one-time lessons or presentations with or without periodic follow-up. As an example, Hubbard et al. involved a 50-minute presentation that addressed risk factors for skin cancer, personal anecdotes from individuals with skin cancer, etc., after which the children were given an informational booklet [60]. In the seven weeks following the presentation, motivational and informational text messages were sent twice weekly in an effort to influence summer behaviors. Similarly, Saridi et al. involved a 45-50-minute interactive educational session with follow-up one year after the intervention [17]. Unfortunately, these studies and several others with similar intervention strategies were unable to affect meaningful behavioral change in children. Among the three main types of intervention (i.e. economic, educational, and environmental), educational interventions were most associated with failure to impact sun-protective behaviors in children. Although educational interventions were utilized in many studies that were successful at modifying behaviors, those that incorporated additional economic (e.g. free sunscreen) or environmental (e.g. adding shaded areas at school) interventions were more likely to achieve change. It is not surprising that solely providing educational materials to children might not be very fruitful. Children might find this type of information uninteresting or forget about it shortly after the information is delivered. Furthermore, children who do wish to alter their behavior may not have the resources to do so. By directly providing sun-protective equipment to children and their families, as in the economic interventions, some of the barriers to obtaining sun-protective equipment are addressed, and parents can have a role in administering such materials to their child. A few studies measured sun exposure via physical skin changes by evaluating the incidence of new sunburns, number of new nevi, and/or change in pigmentation of the skin. The incidence of new sunburns was the most commonly measured and impacted outcome compared to the others. In response to sun exposure, sunburns develop rather quickly and can develop after only one outdoor exposure, whereas skin pigmentation and nevi formation are processes that take time and require more chronic exposure to sunlight. Many of the studies that assessed skin pigmentation and nevi formation failed to demonstrate any significant change in these metrics, likely due to a lack of significant behavioral change and/or insufficient length of study. In the case of Bauer et al., educational and/or economic interventions were administered, and the number of incident melanocytic nevi was measured after a three-year period with no significant difference between groups [36]. In this particular study, the intervention failed to impact sun-protective behaviors, which likely directly affected the success of the intervention in impacting nevi formation. Of the studies that had a positive impact on sun-protective behaviors, a common theme was that changes in behavior were often transient or resulted in minimal change in the development of physical skin findings related to sun exposure. In this discussion of sun protection in children, our primary concern is whether early interventions can reasonably decrease a child’s risk of developing skin cancer later in life. It is encouraging to see that children and their parents are able to adopt sun-protective behaviors with the right intervention; however, it is unclear if these behavioral changes will translate to physical changes in the skin and decreased incidence of skin cancer in the future.

**Conclusion**

It is crucial that children be educated on the importance of sun protection. Although a variety of interventions showed promise in achieving this goal, the challenges associated with adopting behavioral change were evident. This review provides direction for future interventions aimed at improving sun safety in children and illustrates the potential impact that early intervention can have on the incidence of skin cancer in future generations.

**References**

4. Greinert R, Roniol M. Skin cancer—primary and secondary prevention (information campaigns and screening)—with a focus on


Introduction: Nail toxicity represents one of the most common cutaneous adverse effects of both classic chemotherapeutic agents and new oncologic drugs, including targeted treatments and immunotherapy.

Objectives: We aimed to provide a comprehensive literature review of nail toxicities derived from conventional chemotherapeutic agents, targeted therapies (EGFR inhibitors, multikinase inhibitors, BRAF and MEK inhibitors) and immune checkpoint inhibitors (ICIs), including clinical presentation, implicated drugs and approaches for prevention and management.

Methods: Retrieved literature from PubMed registry database was reviewed to include all articles published up to May 2021 relevant to the clinical presentation, diagnosis, incidence, prevention, and treatment of oncologic treatment-induced nail toxicity. The internet was searched for relevant studies.

Results: A wide spectrum of nail toxicities is associated with both, conventional and newer anticancer agents. The frequency of nail involvement, especially with immunotherapy and new targeted agents remains unknown and patients with different cancer types receiving different regimens may develop the same nail disorder, whereas patients with the same type of cancer under the same chemotherapeutic treatment may develop different types of nail alterations. The underlying mechanisms of the varying individual susceptibility and the diverse nail responses to various anticancer treatments need further investigation.

Conclusion: Early recognition and treatment of nail toxicities can minimize their impact, allowing better adherence to conventional and newer oncologic treatments. Dermatologists, oncologists and other implicated physicians should be aware of these burdensome adverse effects in order to guide management and prevent impairment of patients’ quality of life.
Introduction

Nail toxicity represents one of the most common cutaneous adverse effects of both classic chemotherapeutic agents and new oncologic drugs, including targeted treatments and immunotherapy [1]. While drug-associated nail toxicity is almost never life-threatening, it significantly impairs patients’ quality of life, often restricting their daily life and self-care activities.

Dermatologists, oncologists and other implicated physicians should be aware of these burdensome adverse effects in order to guide management and prevent impairment of patients’ quality of life. Early recognition and treatment can minimize the impact of these toxicities, allowing better adherence to conventional and newer oncologic treatments. The aim of this article is to provide a comprehensive literature review of nail toxicities derived from conventional chemotherapeutic agents, targeted therapies (EGFR inhibitors, multikinase inhibitors, BRAF and MEK inhibitors) and immune checkpoint inhibitors (ICIs), including clinical presentation, implicated drugs and approaches for prevention and management.

Materials and Methods

Search Strategy and Study Selection

The retrieved literature was reviewed to include all articles relevant to the clinical presentation, diagnosis, incidence, prevention, and treatment of oncologic treatment-induced nail toxicity. The PubMed registry database was searched for relevant studies published up to May 2021. The literature evidence predominantly comprises case reports, case series and systematic reviews. The following Medical Subject Headings search terms were used: nails, nail changes, nail toxicity; chemotherapy, chemotherapeutic drugs/agents, antineoplastic agents. The “related articles” function in PubMed was used to broaden the search, and all retrieved abstracts, studies and citations were reviewed. In addition, we identified other relevant studies by searching the reference lists of the relevant articles and by contacting known experts in the field. No language restrictions were applied.

Data Extraction

Two reviewers independently assessed all relevant studies and specifically extracted data regarding study design, study population characteristics, inclusion and exclusion criteria, nail toxicity parameters, class of chemotherapeutic drugs and their mechanism of action. The individually recorded decisions of both reviewers were compared and any disagreements were resolved by the other reviewers. Study authors were contacted for additional information when necessary.

Discussion

Conventional Chemotherapeutic Drugs (Figure 1)

Cancer therapy has always been a challenging area in clinical medicine and research. Traditionally, chemotherapeutic drugs work by disrupting specific phases of the cell cycle in actively dividing cancer cells (Table 2). Conventional chemotherapeutic drugs continue to be an important part of cancer management but may cause various cutaneous and appendageal reactions including nail toxicity. Nail involvement in cancer therapy is reported in fragmented literature from all over the world. Although it is mostly of cosmetic concern, at times it may require alteration or modification of the therapy, especially if very painful or functionally debilitating nail toxic effects are present. Pain and associated discomfort impair patients’ quality of life, commonly resulting in the inability to perform daily activities [2].

The nail apparatus is characterized by the presence of continuously dividing nail matrix cells, thus making it an easy target of the antimitotic activity of chemotherapeutics [3]. Nail changes in the context of chemotherapy involve multiple or even all 20 nails and usually appear in a temporal relation with the drug intake, due to an acute insult of the nail matrix epithelium. Effects mostly subside upon withdrawal of the responsible chemotherapeutic agent, but occasionally may persist. Because of the specific kinetics of nail formation and growth, it is important to note that the occurrence of these nail toxic effects is often delayed relative to treatment initiation.

Clinical presentation varies, depending on the nail structure affected and the severity of the insult [4]. In terms of topography, when the nail bed is affected, onycholysis, apparent leukonychia and splinter haemorrhages may be observed. Toxicity targeting the nail matrix may result in the appearance of Beau’s lines, onychomadesis, true leukonychia, slower nail growth, nail thinning, brittle nails and melanonychia. Finally, adverse effects involving the perionychium may result in paronychia and pyogenic granuloma [5, 6]. A combination of the aforementioned nail changes is frequent. The most common nail changes reported in the literature include leukonychia, Beau’s lines, brittle thin nails, and nail hyperpigmentation, which may be diffuse or horizontal [7-10]. Taxanes and anthracyclines are the antineoplastic regimens mostly associated with nail changes. However, considering that a majority of the reported patients were on multiple chemotherapeutic agents, pinpointing the offensive drug was not always feasible. Therefore, a combination of agents was implicated in most cases.

Alkylating Agents

CLASSICAL ALKYLATING: CYCLOPHOSPHAMIDE

Classical alkylating agents attack an alkyl group to the guanine base of DNA and are used to treat leukaemia, lymphoma, Hodgkin disease, multiple myeloma, sarcoma, and
Figure 1. Nail toxicities due to conventional chemotherapeutic drugs. A. Muehrcke’s lines due to treatment with cisplatin: Transversal white lines with healthy nail bed between them. B. Dermoscopic examination of the same patient with clear visualization of the leukonychia in the form of Muehrcke’s lines. C. Red-brown discoloration of the nails associated with painful subungual hematomas and onycholysis following treatment with taxol. D. Dermoscopic image of the chemotherapy-induced central subungual hematoma that differs from traumatic subungal hematoma: note the bright red color with an orange/brown halo (in trauma: dark violet with globular pattern accompanied by transversal whitish line). E. Longitudinal melanonychia following cyclophosphamide treatment. F. Dermoscopy image of the cyclophosphamide-induced melanonychia with a homogenous brown band with absence of Hutchinson or micro-Hutchinson's sign. Borders appear blurry but this may happen in the great toenail due to thickness of the nail plate. This is a false positive sign that should be interpreted together with the clinical history of the patient.

Table 1. Proposed management algorithm for taxane-related onycholysis [38].

| Grade 0* | • Preventive nail care instructions given  
| • Frozen gloves should be considered |
|------------------------|-----------------------------------------------|

| Grade 1* | If asymptomatic separation of the nail bed from the nail plate or nail loss  
| • Continue drug at current dose and monitor for change in severity  
| • Obtain bacterial/fungal cultures if infection is suspected; apply topical antibiotics or fungal agent  
| • Reassess after 2/3 weeks. If reaction worsens proceed to next step |

| Grade 2* | If symptomatic separation of the nail bed from the nail plate or nail loss; Limiting instrumental activities of daily living  
| • Continue drug at current dose and monitor for change in severity  
| • Obtain bacterial/fungal cultures if infection is suspected  
| • If infection, begin oral antibiotics with anti- Staphylococcus aureus and gram-positive coverage  
| • If painful hematoma or subungal abscess is suspected, partial or total nail avulsion is required  
| • Pain control  
| • Reassess after 2 weeks; if reactions worsen or do not improve interrupt treatment until severity decreases to Grade 0-1 |

| Grade 3* | If severe pain and/or superinfection; Limiting self-care activities of daily living  
| Interrupt treatment until severity decreases to Grade 0-1, obtain bacterial/fungal cultures if infection is suspected and continue treatment of nail reaction with the following:  
| • If infection, begin oral antibiotics with anti-Staphylococcus aureus and gram-positive coverage  
| • If painful hematoma or subungal abscess is suspected, partial or total nail avulsion is required  
| • Pain control  
| • Reassess after 2 weeks; if reactions worsen or do not improve, consider dose interruption or discontinuation per protocol and switch to another antineoplastic agent |

*From nail loss clinical grading, Common Terminology Criteria for Adverse Events (CTCAE), V4.02
**Table 2. Conventional chemotherapeutic drugs, mechanism of action and associated nail toxicity.**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Chemotherapeutic Drugs</th>
<th>Mechanism Of Action</th>
<th>Nail Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td>Crosslink with DNA molecules and damage cells in all phases of the cell cycle</td>
<td></td>
</tr>
<tr>
<td>Classical alkylating</td>
<td>Cyclophosphamide</td>
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<tr>
<td>Platinum agents</td>
<td>Cisplatin</td>
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<td></td>
<td>Carboplatin</td>
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<td>Oxaliplatin</td>
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<td><strong>Platinum agents</strong></td>
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<td>Oxaliplatin</td>
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<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
<td>Substitute building blocks of DNA and RNA and damage cells in the S phase</td>
<td></td>
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<tr>
<td>Analogs</td>
<td>Pemetrexed</td>
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<tr>
<td>Fluorouracil</td>
<td>5-Fluorouracil</td>
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<td></td>
<td>Capecitabine</td>
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<td></td>
<td>Tegafur</td>
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<td></td>
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<tr>
<td><strong>Antitumor antibiotics</strong></td>
<td></td>
<td>Intercalate with DNA base pairs and interfere with topoisomerase II in all cell cycle phases</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin</td>
<td></td>
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<tr>
<td>Bleomycin</td>
<td>Daunorubicin</td>
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<td></td>
<td>Epirubicin</td>
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<tr>
<td><strong>Mitotic inhibitors</strong></td>
<td></td>
<td>Prevent the formation of spindles or microtubules during the M phase</td>
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<tr>
<td>Taxanes</td>
<td>Docetaxel</td>
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<td>Vinca alkaloids</td>
<td>Paclitaxel</td>
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<td></td>
<td>Vincristine</td>
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<tr>
<td><strong>Topoisomerase inhibitors</strong></td>
<td>Etoposide</td>
<td>Intercalate with DNA base pairs and interfere with topoisomerase II in all cell cycle phases</td>
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<tr>
<td><strong>Topoisomerase II</strong></td>
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<td>Interfere with topoisomerase I or II during DNA replication in all cells in the S or G2 phase</td>
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<td>Paronychia</td>
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cancers of the lung, breast and ovary [11]. All can be administered intravenously, though cyclophosphamide can be also taken orally [12]. Cyclophosphamide may cause diffuse hyperpigmentation, longitudinal melanonychia, Beau’s lines, onychomadesis, Mees’ lines, Muehrcke’s lines and onycholysis (Table 2).

**Platinum Agents: Cisplatin, Carboplatin, and Oxaliplatin**

Platinum agents form reactive platinum complexes that crosslink with DNA molecules, inhibiting DNA synthesis and repair, and are given intravenously. Cisplatin is an older drug that causes many side effects (eg, ototoxicity, neurotoxicity, nephrotoxicity, and emetogenicity) and is used to treat a wide variety of solid tumors. Cisplatin may cause Beau’s lines, hyperpigmentation or Muehrcke’s lines. Carboplatin and oxaliplatin are newer-generation platinum agents with less toxicity [13]. These chemotherapeutic agents may cause diffuse hyperpigmentation or Muehrcke’s lines (Table 2).

**Antimetabolites**

**Analogs: Pemetrexed**

Pemetrexed is an intravenously administered folate analogue that interferes with enzymes required for pyrimidine and purine synthesis, and is used for the treatment of mesothelioma, non-small cell lung carcinoma (NSCLC), and breast, head, and neck carcinoma. Uncommon reported nail reactions to pemetrexed include melanonychia and onycholysis [14] (Table 2).

**Fluorouracil: 5-Fluorouracil, Capecitabine and Tegafur**

5-Fluorouracil (5-FU) is a pyrimidine analog that inhibits the enzyme thymidylate synthase, thereby interrupting thymidine synthesis required for DNA replication, and can cause myelosuppression, diarrhea, mucositis, and dermatitis [12].

Capecitabine and Tegafur are orally administered prodrugs especially used for colon and gastrointestinal neoplasms. They are designed to be well absorbed from the gastrointestinal tract and converted to 5-FU in the liver or within the tumor at lower concentrations than 5-FU intravenously dosages, thereby minimizing toxicity [15].

In the nails, 5-FU may cause diffuse melanonychia, transverse bands, or half and half-like nails (Lindsay nails), while there have also been reports of onycholysis, paronychia, and thickening of the nail with its use [16]. Capecitabine and tegafur also cause longitudinal melanonychia [16]; however, onycholysis and onychomadesis have only been seen with capecitabine [12] (Table 2).

**Antitumor antibiotics**

**Antihyacinclines: Doxorubicin and Daunorubicin**

The anthracyclines doxorubicin and daunorubicin are derived from the bacterium Streptomyces peucetius var. caesius and are used to treat various hematologic malignancies and solid tumors. Their main adverse effect is cardiotoxicity, which is limited in the liposomal pegylated or encapsulated form of anthracyclines used for non-Hodgkin lymphoma, multiple myeloma, NSCLC, AIDS-related Kaposi sarcoma, and refractory ovarian cancer. Both drugs are administered intravenously [12]. Doxorubicin may cause diffuse hyperpigmentation, Beau’s lines, Mees’ lines or Muehrcke’s lines. Daunorubicin may also cause diffuse hyperpigmentation or Mees’ lines (Table 2).

**Bleomycin**

Bleomycin is a glycopeptide produced by the bacterium Streptomyces verticillus and is used for the treatment of squamous cell carcinoma, lymphoma, testicular carcinoma, and malignant pleural effusion. It can be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or given as an intralesional injection in recalcitrant warts, keloids, and scars [17]. Toxicity to bleomycin occurs in the lungs and skin because these organs lack bleomycin hydrolase, an inactivating enzyme [18]. Pulmonary fibrosis is a serious complication of high doses (>400 units), while cutaneous reactions usually occur between 200 to 300 units [17].

Bleomycin may cause nail dystrophy, and horizontal or vertical nail pigmentation [17] (Table 2).

**Mitotic/Spindle Inhibitors**

**Taxanes: Paclitaxel and Docetaxel**

Taxanes are among the most commonly prescribed anticancer drugs and were initially derived from yew trees. Paclitaxel is a natural extract derived from the bark of the pacific yew tree (Taxus brevifolia) that became commercially available in 1992. On the other hand, docetaxel is a semisynthetic analogue of paclitaxel synthesized from the needles of the European yew tree (Taxus baccata). Both drugs act as antimicrotubule agents by promoting the polymerisation of tubulin into highly stable intracellular microtubules, thus disrupting mitosis and normal cell division, and eventually leading to cell death [19-21]. Because of their highly hydrophobic properties, they require the use of solvents (non-ionic polyoxyethylated castor oil -Cremophor EL®- for paclitaxel; non-ionic surfactant polysorbate 80 for docetaxel) to facilitate parenteral administration. The drugs are approved for a number of indications in the US and Europe. Paclitaxel was the first taxane discovered, is generally administered by weekly infusion (80 mg/m2) and is currently approved by the US Food and Drug Administration for the treatment of breast cancer, NSCLC, AIDS-related Kaposi sarcoma, and ovarian cancer.

Docetaxel, developed later, is infused (100 mg/m2) every three weeks and is used for the management of advanced breast, gastric, NSCLCs, hormone-refractory prostate
cancer, and advanced head and neck squamous cancer [22]. Docetaxel appears to have recently become most specifically associated with nail toxicity, occurring in up to 30 – 40% of patients [6, 23].

Nail changes with taxanes are very common with some series reporting rates as high as 89% after three treatment cycles [24- 29]. These chemotherapeutic agents may cause diffuse hyperpigmentation, Beau’s lines, onychomadesis, Mees’ lines, paronychia, subungual hyperkeratosis, pyogenic granuloma, subungual & splinter hemorrhage, onycholysis/ exudative onycholysis, brittle nails, onychorrhexis or koilonychia (Table 2).

Nab-paclitaxel is a novel, solvent-free, albumin-bound, colloidal suspension (with a size of 130 nm) of paclitaxel that has led to a significant improvement in progression-free survival, median overall survival, and overall response rates in patients with metastatic breast and pancreatic cancers [21, 30]. It has received FDA and EMA approvals for the treatment of certain forms of both cancers [30]. It is also approved in the US for metastatic non-small cell lung cancer and is still under evaluation for several other indications, such as metastatic urothelial tumors [31, 32]. Nab-paclitaxel was developed to circumvent the highly hydrophobic properties of taxanes and to improve intratumoral paclitaxel penetration [30, 33]. Since it is devoid of Cremophor EL® (the solvent for paclitaxel), several significant adverse events such as hypersensitivity reactions are less likely to develop [30]. Nail toxicity has only been sporadically reported with nab-paclitaxel, especially onycholysis, and is easily manageable [34]. The overall incidence of all-grade nail toxic effects with nab-paclitaxel is significantly lower in comparison with paclitaxel or docetaxel (19.4%) (95% CI: 11.8-30.3%) [35].

**Vinca Alkaloids: Vincristine**

Vincas alkaloids were historically extracted from the leaves of the Madagascar periwinkle (Catharanthus roseus). Vincristine has been approved for intravenous use in the United States and is often used in combination chemotherapy regimens because of its lack of myelosuppression. Vincristine is commonly used to treat acute lymphocytic leukemia, multiple myeloma, chronic lymphocytic leukemia, lymphoblastic crisis of chronic myelogenous anemia, sarcomas, and small cell lung cancer with distant metastases [12]. Vincristine may cause diffuse hyperpigmentation, longitudinal melanonychia, Beau’s lines, onychomadesis, Mees’ lines or Muehrcke’s lines (Table 2).

**Topoisomerase Inhibitors**

**Topoisomerase II: Etoposide**

Etoposide is an inhibitor of the enzyme topoisomerase II, which relieves the helical strain during DNA replication by cutting both strands of DNA simultaneously. Topoisomerase II inhibitors frequently induce rearrangements of the mixed lineage leukemia gene and can cause a secondary leukemia side effect [36]. Etoposide has been approved by the US Food and Drug Administration to be used in combination with other medications to treat small cell lung cancer and testicular cancer. It is a derivative of podophyllotoxin. It is typically taken orally, but can also be administered intravenously, though care must be used to prevent extravasation because it is an irritant and can cause tissue damage. Nail toxic side effect caused by etoposide is paronychia [12] (Table 2).

**Targeted Biologic Drugs (Figure 2)**

Targeted cancer therapies are drugs that selectively block specific parts of cancer cells, such as proteins or genes, that help cancers grow and spread. Targeted biologic therapies are well-known causing factors of cutaneous adverse effects, including changes in the nail apparatus [37, 38].

Cutaneous and nail reactions may be attributed to the mode of action of these regimens that target specific molecules that are also expressed in the skin and appendageal epithelium.

**EGFR-Inhibitors**

Epidermal growth factor receptor inhibitors (gefitinib, erlotinib, cetuximab, panitumumab) block the signal transduction pathway, needed for cell proliferation, migration and angiogenesis of tumor cells [37- 40]. Gefitinib and erlotinib are orally administered EGFR tyrosine kinase inhibitors, whilst cetuximab and panitumumab are humanized monoclonal antibodies that are given intravenously. These regimens are used for colorectal cancer, breast cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, and head and neck squamous cell carcinoma (SCC) [38- 40]. A common nail reaction in the context of EGFR inhibition is paronychia, representing the second most frequent skin toxicity induced by EGFR after papulopustular eruption [41]. It involves the nails and the digits, with the first digit being the site most commonly affected. Other ungual adverse reactions include discoloration, pitting, nail thinning/fragility (inhibition of nail matrix keratinocytes), periungual pyogenic granuloma (an overgrowth of granulation tissue and a formation of painful, bleeding nodule), cracked and swollen nail folds and cuticles, partial or complete loss of nails and ingrowth of nails [37, 38] (Table 3). The aforementioned alterations may appear 1 to 2 months after treatment initiation and affect about 15% of patients [38]. Secondary infection is not unusual and in this scenario, a culture swab is recommended. In patients treated with Cetuximab that developed paronychia, Staphylococcus aureus was found in 23%, while 31% had coagulase-negative, Gram (+) bacteria (nosocomial colonization) [37, 38]. Prevention of superinfection was achieved.
Bruton’s Tyrosine Kinase (BTK) Inhibitors

Bruton’s tyrosine kinase inhibitor, ibrutinib, is a small molecule that binds to a protein, important in B-cells. It is used for the treatment of chronic lymphocytic leukemia, Waldenström’s macroglobulinemia, refractory and relapsed mantle-cell lymphoma. Brittle nails are the most common nail change, seen in about 2/3 of treated patients, followed by onychoschizia, onychorrhexis and mild onycholysis [38] (Table 3).

Anti-HER2/Anti-HER

Anti-human epidermal growth factor receptor 2 (Anti-HER2) is a class of medicines used to treat all stages of HER2-positive breast cancer, from early-stage to metastatic disease. Trastuzumab was shown to cause thin nails [37, 38]. lapatinib (breast cancer and solid tumors), afatinib (NSCLC) and dacomitinib (NSCLC), besides thin nails, may induce nail reactions such as paronychia, pyogenic granuloma, slower growth rate and mild onycholysis [38] (Table 3).

Anti-MEK

Mitogen-activated protein kinase enzymes MEK1 and/or MEK2, trametinib (metastatic melanoma), cobimetinib (melanoma) and selumetinib (Neurofibromatosis type 1 with antibacterial soaks (chlorhexidine or vinegar in water) [38]. Warm compresses, silver nitrate, topical corticosteroids and systemic tetracyclines are recommended in order to reduce periungual inflammation, depending on the grade of the toxicity.

Angiogenesis-Inducing Inhibitors

Sorafenib and sunitinib are multikinase inhibitors that specifically target tumor cell angiogenesis and proliferation via VEGFR (vascular endothelial growth factor), PDGFR (platelet-derived growth factor receptor) and other kinases [38]. Sorafenib is indicated in renal cell carcinoma, non-small cell lung cancer, hepatocellular carcinoma, melanoma, pancreatic and colon cancers, whilst sunitinib is prescribed for renal cell carcinoma, breast cancer, colon cancer and gastrointestinal stromal tumor. Both are orally administered. Studies report that during the first 2 months of therapy, 70% and 25% of patients taking sorafenib and sunitinib, respectively, developed fingernail subungual splinter hemorrhages [41] (Table 3). The latter resolved spontaneously without treatment. This may be linked to the role VEGFR play in the renewal of capillaries and their sustain despite frequent injuries at the distal fingers, which is now inhibited due to sorafenib and sunitinib intake [38, 41].

Figure 2. Nail toxicities due to targeted biologic drugs. A. Paronychia due to treatment with EGFR tyrosine kinase inhibitor (panitumumab) for colorectal cancer: proximal nail fold is painful, erythematous and swollen with presence of oozing and crusting. B. Same patient as a.: close-up to a pyogenic granuloma that frequently accompanies paronychia due to EGFR inhibitors. C and D. Clinical and dermoscopy image of brittle nails during EGFR inhibitor therapy for lung cancer. The nail plate is fragile and the surface of the nail presents longitudinal fine fissures while the distal edge of the plate appears to crumble and is not sharply delineated. In dermoscopy presence of splinter hemorrhages can also be detected. E and F. Acute photo-onycholysis in a melanoma patient treated with BRAF inhibitors: clinical and dermoscopic image. The nails were extremely painful with almost total detachment of the nail plate and presence of oozing and subungual hematoma.
complex, certain types of seizures in adults and children and prevention of transplant rejection), as well as temsirolimus (indicated in renal cell carcinoma), may cause yellow nail discoloration, paronychia, pyogenic granuloma, slower growth rate-thin nails, mild onycholysis and brittle nails [38, 41].

**M-TOR Inhibitors**

The mammalian target of rapamycin regulates cellular metabolism, growth and proliferation by forming and signaling through two protein complexes, mTORC1 and mTORC2 [38]. Everolimus (indicated in advanced renal cell carcinoma, advanced breast cancer, pancreas, stomach, intestines, lungs, subependymal giant cell astrocytoma, tuberous sclerosis complex, certain types of seizures in adults and children and prevention of transplant rejection), as well as temsirolimus (indicated in renal cell carcinoma), may cause yellow nail discoloration, paronychia, pyogenic granuloma, slower growth rate-thin nails, mild onycholysis and brittle nails [38] (Table 3).

**RET Inhibitor**

RET inhibitors are targeted therapies used on tumors characterized by activated alterations in the RET proto-oncogene. These include non-small cell lung cancer (NSCLC), medullary thyroid cancer and papillary thyroid cancer.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Target</th>
<th>Chemotherapeutic Drugs</th>
<th>Nail Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-EGFR</td>
<td>EGFR (HER1 or ErbB1)</td>
<td>Cetuximab Panitumumab, Erlotinib Gefitinib Necitumumab</td>
<td>Paronychia Pyogenic granuloma Slower growth rate Mild onycholysis Thin nails Brittle nails</td>
</tr>
<tr>
<td>Anti-HER2</td>
<td>HER2</td>
<td>Trastuzumab</td>
<td>Thin nails</td>
</tr>
<tr>
<td>Anti-HER</td>
<td>HER1-4 (ErbB1-4)</td>
<td>Lapatinib Afatinib Dacomitinib</td>
<td>Paronychia Pyogenic granuloma Slower growth rate Mild onycholysis Thin nails Brittle nails</td>
</tr>
<tr>
<td>Anti-MEK</td>
<td>MEK 1/2</td>
<td>Trametinib Cobimetinib Selumetinib</td>
<td>Paronychia Pyogenic granuloma Slower growth rate Mild onycholysis Brittle nails</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>mTOR</td>
<td>Everolimus Temsirolimus</td>
<td>Paronychia Pyogenic granuloma Yellow nail discoloration Slower growth rate-thin nails Mild onycholysis Brittle nails</td>
</tr>
<tr>
<td>Angiogenesis multikinase inhibitors</td>
<td>VEGFR 1-3 PDGFR α/β and other molecular targets</td>
<td>Sunitinib Sorafenib Cabozantinib Axitinib Pazotinib Regorafenib</td>
<td>Splinter subungual hemorrhage Brittle nails</td>
</tr>
<tr>
<td>RET inhibitor</td>
<td>EGFR VEGFR 2/3 RET</td>
<td>Vandetanib</td>
<td>Paronychia Pyogenic granuloma Photoonycholysis Splinter subungual hemorrhage</td>
</tr>
<tr>
<td>BCR-ABL inhibitor</td>
<td>BCR-ABL c-KIT PDGFR</td>
<td>Imatinib</td>
<td>Melanonychia Lichenoid reactions</td>
</tr>
<tr>
<td>Bruton inhibitors</td>
<td>Bruton tyrosine kinase</td>
<td>Ibrutinib</td>
<td>Brittle nails Onychoschizia Onychorrhexis Mild onycholysis</td>
</tr>
</tbody>
</table>

**Table 3. Main nail toxicities induced by targeted anticancer therapies** [38].
Vandetanib is an oral multikinase inhibitor which targets the RET, proto-oncogene, EGF and VEGF receptors. The most prevalent nail adverse event associated with Vandetanib therapy is subungual hemorrhage (due to VEGF inhibition), paronychia/pyogenic granuloma (EGFR inhibition) and a painful type 1 photo-onycholysis [38] (Table 3). Patients should be informed about UVA/UVB photo-protection.

**BCR-ABL Inhibitors**

BCR-ABL is a gene produced by the BCR gene and the C-ABL proto-oncogene and is considered to be the main cause of chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL) that are Philadelphia chromosome-positive, certain types of gastrointestinal stromal tumors, hypereosinophilic syndrome, chronic eosinophilic leukemia, systemic mastocytosis and myelodysplastic syndrome [38]. **Imatinib** is an oral medication of this group that may induce melanonychia and lichenoid reactions (Table 3). Melanonychia appears 1-2 months after treatment initiation. It results from the direct toxic action of the regimen on the melanocytes of the nail matrix, with secondary melanin production. Melanonychia striate, as well as total melanonychia do not require any treatment. They regress spontaneously several months after treatment discontinuation [38]. Lichenoid reactions are very rare but may provoke a destruction of the matrix and a subsequent scar formation.

**Immunotherapy (Figure 3)**

The immune system, as part of its normal function, detects and destroys abnormal cells and prevents or suppresses cancer growth. Despite that, cancer cells have ways to evade the immune system. They may present genetic changes that make them less visible to the immune system, have proteins on their surface that turn off immune cells or affect the normal cells surrounding a tumor in a way that they interfere with the immune response to cancer cells.

The most prevalent immune-related dermatologic adverse events (irAE) are triggered by immune checkpoint inhibitors (CPIs).

**Immune Checkpoint Inhibitors** (CPIs) are targeted molecules that modulate the immune system, assist with self-tolerance, and minimize collateral tissue damage when immune responses are activated. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more efficiently to cancer. This blockade has been associated with autoimmune-like toxicities, named immune-related adverse events (irAE) [24, 43].

![Figure 3. Nail toxicities due to immunotherapy.](image)
Immune checkpoints include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). The CTLA-4, PD-1, and PD-L1 pathways mediate immune responses at different levels. CTLA-4 controls the amplitude of immunologic response at early stages of T-cell activation, whereas PD-1 and PD-L1 pathways act at later stages, limiting T-cell activity in the peripheral tissues. By activating cytotoxic CD4+/CD8+ T cells, immune checkpoint blockade therapy shifts the immune system towards anti-tumor activity [42-44].

The etiopathogenetic mechanism seems to be connected to the T-cell activation, mediated by the blockade of PD-1/PD-L1 and CTLA-4 receptors.

CPIs include anti-PD-1 (nivolumab and pembrolizumab) and anti-CTLA-4 (ipilimumab, tremelimumab) agents, as well as the newly developed anti-PD-L1 agents (atezolizumab, durvalumab, avelumab) [42-44].

ICIs nail alterations have not been systemically investigated and are considered uncommon. Nail toxicity presents late in time, with an onset extended up to several months from ICI initiation [42, 43].

Persistence of the nail change after ICI discontinuation has been also reported.

Diverse nail changes have been reported in relationship to ICIs, including onycholysis, onychomadesis, longitudinal fissures, onychorrhexis, layered splitting of the nail plate, lunular erythema, thinning of the nail plate and fragility. Commonly, more than one finger- or toenails are involved. Nail psoriasis is the most common immunotherapy-related toxicity [42, 45].

Since the majority of nail alterations appear in conjunction with psoriasiform or lichenoid rashes, they are most probably of the same nature. In line with this theory are the histopathologic alterations found in two patients exhibiting onycholysis that were consistent with lichenoid reaction. This develops either as a deterioration of pre-existing nail psoriasis, or as a de-novo appearance. Histopathologically confirmed psoriasis of the nail has been described in association with nivolumab, clinically characterized by nail thickening combined with periungual erythema [43, 45].

First-line treatment for these nail changes is topical therapy. If topicals fail and there is also skin involvement, systemic therapy should be considered [43, 45].

Pathogenesis of certain nail changes and potentially responsible anticancer drugs. Table 4 highlights the diagnostic challenges related to drug-induced nail toxicities.

**Melanonychia**

Melanonychia represents one of the most common adverse effects of chemotherapeutic agents. Saraswat et al. [4] and Pavey et al. [1] found nail hyperpigmentation as the most common nail toxicity of chemotherapeutic drugs. This pigmentation develops after 1–2 months of treatment and is proposed to be the outcome of matrix melanocyte activation, which usually affects several nail plates. Nail melanocytes are quiescent and generally do not produce melanin. Melanonychia results from the direct toxic action of chemotherapy on the melanocytes of the nail matrix, with secondary melanin production analogous to that of post-inflammatory hyperpigmentation seen in the skin [46-49].

The activation of a subgroup of melanocytes produces a single or several longitudinal pigmented bands (melanonychia striata) whereas diffuse activation of melanocytes gives rise to diffuse nail pigmentation (total melanonychia). Transverse melanonychia may also be observed [2]. Skin or mucosal pigmentation changes are frequently associated.

Nail hyperpigmentation is more often reported with chemotherapeutic agents like cyclophosphamide, cisplatin, fluorouracil and its prodrug capecitabine, taxanes, doxorubicin, bleomycin and Imatinib [16, 38, 50–54] (Table 5).

Chemo-induced hyperpigmentation does not require any treatment and progressively regresses several months after treatment discontinuation. For patients who would like to conceal this melanonychia, dark-colored nail polish may be proposed.

**Beau’s Lines**

Beau’s lines correspond to the formation of transverse linear depressions in the dorsum of the nail plate and result from a transitory decrease in mitotic activity of the proximal nail matrix keratinocytes. The depth of the groove is strictly

**Table 4. Challenges in the diagnosis of drug-induced nail toxicity.**

<table>
<thead>
<tr>
<th>Several factors may pose diagnostic difficulties in the scenario of drug-induced nail toxicity [2, 3, 7, 81]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nail changes may appear several weeks after drug intake, due to the kinetics of nail formation and the slow growth rate of the nail plate</td>
</tr>
<tr>
<td>2. Patients are often on multiple potentially causative medications</td>
</tr>
<tr>
<td>3. Symptoms often improve or resolve without drug withdrawal</td>
</tr>
<tr>
<td>4. Rechallenge is commonly uneventful</td>
</tr>
<tr>
<td>5. Non-drug causes may be involved</td>
</tr>
<tr>
<td>6. Abnormalities do not necessarily involve all nails</td>
</tr>
<tr>
<td>7. Poor understanding of the pathogenesis of nail damage.</td>
</tr>
</tbody>
</table>
Table 5. Nail changes presented in association with the potentially responsible anticancer regimen.

<table>
<thead>
<tr>
<th>Nail Changes</th>
<th>Conventional Chemotherapeutic Drugs</th>
<th>Targeted Chemotherapeutic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse hyper-pigmentation</td>
<td>Cyclophosphamide, vincristine, cisplatin, carboplatin, oxaliplatin, 5-fluorouracil, capecitabine, doxorubicin, daunorubicin, bleomycin, hydroxyurea, busulfan, docetaxel, paclitaxel, pemetrexed, etoposide combination of cyclophosphamide/adriamycin/ vincristine/cyclophosphamide/adriamycin/ docetaxel</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Longitudinal melanonychia</td>
<td>Cyclophosphamide, vincristine, bleomycin, tegafur, combination of cyclophosphamide/adriamycin/vincristine</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Beau's lines</td>
<td>Docetaxel, paclitaxel, cisplatin, doxorubicin, bleomycin, vincristine/cyclophosphamide/docetaxel</td>
<td></td>
</tr>
<tr>
<td>Onychomadesis</td>
<td>Paclitaxel, docetaxel, capecitabine, combination of cyclophosphamide/vincristine/procarbazine/ prednisolone</td>
<td></td>
</tr>
<tr>
<td>Mees’ lines</td>
<td>Cyclophosphamide, doxorubicin, vincristine, docetaxel, paclitaxel, combination of cytarabine/ daunorubicin cyclophosphamide/doxorubicin/vincristine/ prednisolone (CHOP)</td>
<td></td>
</tr>
<tr>
<td>Muehrcke’s lines</td>
<td>Combination of cyclophosphamide/doxorubicin/5-fluorouracil vincristine/doxorubicin/dexamethasone cisplatin, oxaliplatin</td>
<td></td>
</tr>
<tr>
<td>Half and half nails</td>
<td>5-Fluorouracil</td>
<td></td>
</tr>
<tr>
<td>Onycholyisis</td>
<td>Docetaxel, paclitaxel, cyclophosphamide, pemetrexed, 5-fluorouracil, capecitabine</td>
<td>Cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, ibrutinib, vandetanib</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Fluorouracil, docetaxel, paclitaxel, etoposide</td>
<td>Cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, vandetanib</td>
</tr>
<tr>
<td>Subungual hyperkeratosis</td>
<td>Docetaxel, paclitaxel, fluorouracil</td>
<td></td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>Docetaxel, paclitaxel</td>
<td>Cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, vandetanib</td>
</tr>
<tr>
<td>Subungual &amp; splinter hemorrhage</td>
<td>Docetaxel, paclitaxel</td>
<td>Vandetanib, sunitinib, sorafenib, caboazantinib, axitinib, pazotinib, regorafenib</td>
</tr>
<tr>
<td>Brittle nails</td>
<td>Docetaxel, paclitaxel</td>
<td>Cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus temsirolimus, ibrutinib, sunitinib, sorafenib, caboazantinib, axitinib, pazotinib, regorafenib</td>
</tr>
<tr>
<td>Onychorrhexis</td>
<td>Docetaxel, paclitaxel</td>
<td>Ibrutinib</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>Docetaxel, paclitaxel</td>
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</table>
correlated to the extent of nail matrix damage. The width is proportional to the duration of the insult. Beau’s lines have been described with nearly all chemotherapeutic agents, especially when used in combination or with a high-dose regimen. They are probably the most frequent nail changes noted in patients exposed to chemotherapy [46-48]. Beau’s lines often affect all nails but are more frequent in fingernails and appear after a few weeks of chemotherapy [4, 55]. After repeated courses of chemotherapy, several depressions can be noted in the same nail. They move distally with nail growth. The presence of regular transverse Beau’s lines in the nail plate reflects the temporary cessation of matrix proliferation during each chemotherapy cycle. Chemotherapeutic agents such as docetaxel, paclitaxel, a combination of epirubcin/vincristine/cyclophosphamide, and cyclophosphamide/doxorubicin/fluorouracil are associated with Beau’s lines [4, 56, 57] (Table 5).

Onychomadesis

Onychomadesis is a spontaneous separation of the nail plate from the nail bed in its proximal portion. It implies a limited lesion affecting the proximal part of the matrix. It results from temporary cessation of nail growth lasting for more than 2 weeks. Initially, a small cleavage appears under the proximal portion of the nail. This forms a shallow ulcer that does not involve the deeper layers. When the injury is healed, the nail regrows over again distally. In latent onychomadesis, the nail plate demonstrates transverse split because of complete inhibition of nail growth for 1–2 weeks. Beau’s lines may evolve into the formation of onychomadesis, which essentially corresponds to the extreme form of Beau’s lines. The nail plate is then divided into two parts by a transverse thick groove, which remains latent for a long period before the nail plate ultimately sheds [58]. Onychomadesis induced by chemotherapeutic agents is thought to be the result of arrested mitotic activity in the nail matrix resulting in nail separation and shedding [59, 60].

Onychomadesis induced by chemotherapeutic agents was originally described by Kochupillai et al [61]. Since then only five cases have been reported in the literature. In Saraswat et al. the drugs associated with the development of onychomadesis were imatinib, paclitaxel, capecitabine, and a combination of cyclophosphamide/vincristine/procarbazine/prednisolone (Table 5).

Leukonychia

Leukonychia is characterized by white discoloration of a part of the nail plate or the complete nail plate, and can be divided into true leukonychia and apparent leukonychia. Leukonychia induced by chemotherapeutic agents usually occurs in the form of apparent leukonychia [10, 46-48, 62].

True Leukonychia (white opaque coloration - total or transverse: Mees’ lines) results from altered keratinization of the distal nail matrix. Parakeratotic nuclei are retained in the nail plate and thus the nail appears opaque and white in color owing to the diffraction of light by parakeratotic cells. True leukonychia does not disappear with pressure and moves distally as the nail grows. Mees’ lines are transverse white, non-blanching parallel lines to the lunula across the entire nail bed and have no palpable ridges [63, 64]. In chemotherapy-induced true transverse leukonychia, the sessions of transverse white bands and the distance between them seemed to coincide with the number and duration of chemotherapy cycles, respectively.

Apparent Leukonychia (white transparent coloration) is observed because of changes in the nail bed vasculature on pressure, visible through the translucent nail plate. True and apparent leukonychia may be differentiated clinically by diascopy. The whitish discoloration disappears (or fades) with digital compression and is not modified by nail growth. Apparent leukonychia can present as three different clinical types: Muehrcke’s lines (the most frequent form in association with chemotherapy), Half and half nails (Lindsay’s nails), or Terry’s nails.

a. Muehrcke’s Lines (the most frequent form in association with chemotherapy) are present as multiple, paired, transverse, whitish bands, parallel to the lunula. Chen et al. [6] found Muehrcke’s lines as the most common nail toxicity of chemotherapeutic drugs in children. This change is commonly seen after chemotherapy and in chronic hypoalbuminemia of less than 2 mg/dl (seen in nephrotic syndrome, glomerulonephritis, liver disease, and malnutrition), and is commonly found on the second, third, and fourth fingernails. Thumbnail involvement is rare. The lines tend to resolve with correction of hypoalbuminemia. The exact pathogenesis is unknown, but the suggested reasons are edema of the nail bed, which occurs due to hypoalbuminemia, and an alteration of nail plate attachment to the nail bed, which occurs due to vascular compromise following chemotherapy [6].

b. Half and Half Nails (Lindsay’s nails) where there is a definite border between the proximal area (opaque white) and the distal area (pink or reddish brown) occupying 20%–60% of the nail bed. Distal red-brown pigmentation does not fade with pressure.

c. Terry’s Nails, where the whole nail appears white, except a 1–2 mm pink-to-brown distal band, and the lunula may or may not be visible.

In most cases, leukonychia involves all fingernails and may coexist with melanonychia. It has been described in association with numerous chemotherapeutic agents but
generally develops when chemotherapy is used in combination. Systematic screening for associated hypoalbuminemia should be performed in this context.

Mees’ lines are usually observed with the use of docetaxel and a combination of cytarabine/daunorubicin and cyclophosphamide/doxorubicin/vincristine/prednisolone [65-67] (Table 5).

Muehrcke’s lines have been reported with cisplatin, oxaliplatin and a combination of cyclophosphamide/doxorubicin/5-fluorouracil and vincristine/doxorubicin/dexamethasone [68] (Table 5).

Nail growth is faster in children and adolescents, and is estimated to be at a rate of 0.12 mm/day [23]. However, chemotherapy-induced nail changes in children, in comparison to adult cases, are less well characterized in the literature. Reviewing the limited case reports, transverse leukonychia seems to be the most frequently described nail change in children receiving chemotherapy, with doxorubicin/daunorubicin, vincristine and cyclophosphamide being the main causative agents [23,66].

Onycholysis

Onycholysis is defined by the separation of the nail plate from the underlying nail bed [48]. It usually starts from the distal portion of the nail bed, progresses proximally, and can involve the entire nail with the formation of a space. This may result in the formation of painful subungual abscesses and hemorrhages and finally loss of the nail plate. It is noteworthy that the chemotherapeutic agents that most frequently induce nail changes are taxanes: docetaxel and paclitaxel, resulting from a direct toxic effect [22,25,26,46,59].

However, mild to moderate onycholysis may also be noted with other chemotherapeutic agents as well (capcitabine, etoposide, cytarabine, cyclophosphamide, doxorubicin, or combination therapy) [24,46,48]. The targeted chemotherapeutic agents, which may cause onycholysis are cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacominib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, ibrutinib and vandetanib [38] (Table 5).

Onycholysis is one of the most prevalent adverse events induced by docetaxel or paclitaxel [22]. Recently, the overall incidence of taxane-induced nail toxicity has been systematically investigated [35]; all-grade incidence was 43.7% with paclitaxel (95% CI: 18.0-73.3%) and 34.9% (95% CI: 29.9-40.2%) with docetaxel. For the latter, the relative risk was 77.74 (95% CI: 41.88-144.32; p<0.001) as compared to controls [22].

Nail changes are evident after several weeks of treatment because of the slow growth rate of the nail plate [29]. The development of nail changes is strongly associated with weekly administration, the number of chemotherapy cycles given and the cumulative dose of taxanes [29,46,47,59]. Although it is more common in patients receiving the once-weekly regimen, it can also be observed with the every 3-week regimen [29,46].

The onycholytic portion of the nail plate becomes opaque, loses its translucency, and can take on a white, black, or brown-red color, depending on the type of lesion [57,59,60]. The fingernails are more often involved than toenails and the number of digits affected varies, although involvement may also be diffuse [29,59,69-72]. Onycholysis is initially asymptomatic; however, pain may occur due to acute trauma, progression of the detachment, or development of subungual hemorrhagic blisters or abscesses with purulent malodorous discharge (exudative onycholysis) [22,26,48,60,71]. Secondary bacterial or fungal infections may also develop because of the debris collected in the ventral part of the detached plate. Cosmetic and functional impacts depend on the number of nails involved, the severity of the detachment, and the extent of pain [29].

Taxane-related onycholysis is sometimes associated with inflammatory erythema of dorsal hands or the perimalleolar and Achilles’ areas (PATEO syndrome: periarticular thenar erythema with onycholysis) [22,24].

The changes may affect both the nail matrix (melanonychia, true leukonychia, Beau’s lines and onychomadesis, brittle nails with ridging and thinning, onychorrhexis, koilonychia), the nail bed (onycholysis and apparent leukonychia) or the periungual tissue (paronychia or pyogenic granuloma), may also be affected at the same time with taxane chemotherapy [22,24,26,47].

The pathophysiological origin of taxane-induced onycholysis is not clearly established. It may be the result of direct cytotoxic damage to the nail matrix and epithelial cells of the nail bed with epidermolysis and the secondary loss of adhesion of the nail plate to the nail bed [24,47]. An intrinsic antiangiogenic activity of taxanes has also been postulated [22]. Similarly, a phototoxic mechanism for phototo-onycholysis has been advanced by some authors but remains to be confirmed [59]. Lastly, unilateral onycholysis has been reported in patients suffering from contralateral peripheral palsy, suggesting a taxane-induced neurotropic effect (neurogenic or prostaglandin-mediated inflammation) [73].

More recently, Schepisi et al. [34] hypothesized that paclitaxel-related onycholysis may be directly correlated to the duration of the infusion. Indeed, onycholysis may develop more frequently with a shorter infusion (1 hour) than with a prolonged infusion, because of increased systemic exposure to the Cremophor vehicle (paclitaxel solvent). That may explain, at least in part, the higher incidence seen in patients receiving the weekly paclitaxel regimen (1-hour infusion) in comparison with the every 3-week regimen (3-hour infusion).
The impact of taxane-related onycholysis on the quality of life and daily activities varies; effects depend on the number of digits involved, the degree of detachment, and the extent of pain and if significant it can result in treatment interruption [28, 29]. Therefore, management of onycholysis depends on the clinical grading (i.e., National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) v4.02) and impact on activities of daily living [38] (Table 1). Onycholysis is slowly reversible after treatment, however chronic onycholysis can lead to nail bed keratinization and persistent subungual hyperkeratosis [22, 74]. Therefore, it is crucial to promote nail reattachment as early as possible by preventing further toxicity and treating underlying infections, otherwise onycholysis may become permanent.

Paronychia
Paronychia is the result of inflammation of proximal/lateral nail folds with erythema, edema, tenderness or pain of the nail folds and impaired activity. It usually develops soon after intake of the drug, involves one or several nails and is thought to be the result of the toxic effect of the drug on nail epithelium [2, 8]. Paronychia is a frequent but uncommonly reported adverse effect of epidermal growth factor inhibitors which is the result of aberrant vascular response affecting nail folds [75, 76]. Except for anti-EGFR targeted therapy, RET inhibitor, mTOR inhibitors, anti-MEK, anti-HER, 5-fluorouracil and docetaxel have been reported to develop paronychia as well [4] (Table 5).

Brittle Nails and Decreased Nail Growth
A decrease in nail plate growth is commonly noted with chemotherapy, although it will usually go unnoticed by patients or physicians. The nails are often fragile and thinner, which can lead to koilonychia, onychorrhexis, or onychoschizia after several cycles of chemotherapy [74]. Chemotherapeutic agents such as cetuximab, panitumumab, erlotinib, gefitinib, necitumumab, lapatinib, afatinib, dacomitinib, trametinib, cobimetinib, selumetinib, everolimus, temsirolimus, irbutilinib, sunitinib, sorafenib, cabozaatinib, axitinib, pazotinib, regorafenib, docetaxel and paclitaxel are associated with brittle nails (Table 5).

Koilonychia is a common nail dystrophy in which the dorsal surface of the nail plate becomes flat or truly concave. It is derived from the Greek word koilos, meaning hollow.

Pathogenesis of koilonychia is not known but it is suggested that anoxia and atrophy of the distal matrix are contributory. Koilonychia is the converse of clubbing and it is more appreciated when viewed from the side. When a drop of water is put on the surface, it will not fall off. It should be noted that nails in koilonychia are brittle. It is commonly seen in fingernails rather than toenails. Docetaxel and Paclitaxel may cause koilonychia more often (Table 5).

Onychorrhexis is a type of longitudinal groove wherein a series of shallow and narrow furrows are present running parallel on the nail surface. Docetaxel, paclitaxel and ibrutinib may cause onychorrhexis (Table 5).

Onychoschizia is clinically characterized by the splitting of the nail plate at the free edges in the fingers and toes. It may be localized or the full length of the free edge may be involved. Electron microscopy reveals horizontal separation of the nail plate, which may, sometimes, extend up to the proximal nail fold. It also demonstrates individual cells lying in the empty spaces. These observations indicate lamellar splitting in onychoschizia occurs between the cell layers.

Management and Prevention
Counselling for the prevention of nail toxic effects is mandatory. Healthcare professionals should provide patients with clear and detailed information. The patients should avoid repeated trauma or pressure on nails and nail beds or irritant regimen, including manipulation of the cuticles and nail biting, use of fingernails as “tools,” prolonged soaking in water, exposure to solvents or hard chemicals, and application of artificial nails. They are encouraged to trim their nails regularly and smooth the edges. The nails should be straight/squared and not too short. Prophylactic measures include the use of cotton gloves, comfortable wide-fitting footwear and cotton socks. Housework should be performed only with glove protection. When UV-associated toxicity is related to the drug regimen patients should be informed and wear gloves when outside. Nail lacquers are recommended to limit water loss from the nail plate (especially for brittle nails). Furthermore, daily use of topical emollients on the total nail apparatus (cuticles, plate, and periungual folds) is a prophylactic management for chemotherapy-induced nail toxicity [48]. In addition, Scotté et al. [25] have demonstrated that the preventive use of frozen gloves/socks in patients treated with docetaxel allowed a significant reduction in changes from 51% to 11% (p=0.0001) in fingernails, and from 21% to 0% in toenails, with a trend towards a prolongation (albeit non-significant) of the median time to development of these lesions. Importantly, the Grade 2 or greater nail AEs were reduced from 22% to 0% (p=0.0001) [25, 69]. Therefore, the preventive use of frozen gloves/socks should be advised in patients treated with taxanes [25]. Alternatively, the use of ice packs may be a less expensive and effective strategy with similar efficacy [27]. In addition to preventing nail toxicities, frozen gloves or ice packs have been shown to decrease the incidence of peripheral neuropathy, another potentially dose-limiting adverse event. It is intriguing that despite the simplicity and effectiveness of this intervention, it is not universally employed.

In case onycholysis develops, excising the nail plate (partially or totally) may be necessary (Figure 4), especially in severe and painful lesions, or when associated with a pressure
Cryotherapy’s effect is related to cold-induced vasoconstriction, which reduces the quantity of drugs reaching the proliferating stem cells. For patients who can afford them, tolerate discomfort and exhibit compliance, these prophylactic managements of taxane-induced nail toxicity can be suggested as an option to improve patients’ quality of life and functional statuses. However, future investigations and studies are needed to establish the routine usage protocols, standard outcome measures, long-term efficacy and safety for these interventions [77].

Conclusions
A wide spectrum of nail toxicities has so far been described in association with both, conventional and newer antican
cer agents; however, less importance has been given to nail changes as compared to other skin toxicities. Considering
that nail toxicity is indeed almost never life-threatening, discontinuation of oncologic therapy is only rarely necessary. However, drug interruptions or dose modifications may be warranted, mostly due to serious impairment of patients’ quality of life. Management is primarily directed at symptom control and relief of the patient. Nail changes that result from matrix interruption of blood flow often induce cosmetic changes (not requiring intervention), with the nail eventually growing out normally after treatment discontinuation. On the other hand, nail changes due to disruption of the nail folds frequently require therapeutic intervention, and depending on the severity, also dose modifications.
At present, there is a paucity of data regarding nail involvement and its impact on the functional and emotional status of the patient, during the course of the diverse oncologic treatments. The frequency of nail involvement, especially with immunotherapy and new targeted agents, remains unknown.

Based on the literature, it has been observed that patients with different cancer types receiving different regimens may develop the same nail disorder, whereas patients with the same type of cancer under the same chemotherapeutic treatment may develop different types of nail alterations. The underlying mechanisms of the varying individual susceptibility and the diverse nail responses to various anticancer treatments need further investigation. It is critical to improve our understanding of the underlying pathogenesis of nail toxicity and potential risk factors in order to develop effective evidence-based management strategies, maintain patients' health-related quality of life and ensure optimal dosing of potentially life-prolonging anticancer therapy.

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Introduction: A peripheral rim of globules represents a marker of the horizontal growth phase in nevi and is a common feature in children and adolescents. The observation of melanocytic lesions with peripheral globules (MLPGs) in adulthood deserves more attention, since melanoma may exhibit this feature, albeit rarely. Risk-stratified management recommendations considering a global clinical approach are still missing.

Objectives: To analyze current knowledge on MLPGs and propose an integrated management algorithm stratified for age groups.

Methods: We conducted a narrative review of current published data on MLPGs, analyzing clinical dermoscopic and confocal distinguishing features of melanoma from benign nevi.

Results: The risk of finding a melanoma when removing an MLPG increases with age, especially in people >55 years old, and is significantly higher in the extremities, head/neck and in case of a single asymmetrical lesion, ≥6 mm in diameter. Dermoscopic features associated with melanoma diagnosis include atypical peripheral globules, asymmetrical distribution, multiple rims as well as the reappearance of globules after prior loss. In addition, wide blue-grey regression areas, atypical networks,
Introduction

A dermoscopic subset of melanocytic lesions is characterized by the presence of round to oval globules regularly distributed at the edge of the lesion, representing a marker of the horizontal enlargement with a mean growth rate of 0.25mm²/month [1,2]. A decreased density or a complete disappearance of peripheral globules has been associated with a stabilization of nevi, with an estimated median time of growth cessation of 58.6 months (4-5 years) [1,3]. Enlargement of nevi is commonly observed in children and adolescents with a linear age-related prevalence reduction [3,4]. The common approach towards melanocytic lesions with peripheral globules (MLPGs) in patients younger than 35 years is conservative, not requiring interventions, as regards their benign clinical behavior [2,3]. The occurrence of MLPGs in adulthood and the elderly is infrequent and requires a cautious approach, since change over time represents a suspicious feature [3]. Furthermore, peripheral globules may also be detected, albeit rarely, in melanoma [3,5]. In 2007, the International Dermoscopic Society recommended that MLPGs exhibiting asymmetry of structures within the lesion should be closely monitored or excised, regardless of age [6]. Afterwards, it has been suggested to monitor MLPGs in the absence of other dermoscopic melanoma-specific criteria beyond the age of 30, considering instead surgical excision or close follow-up for those over 50 [3].

Reflectance confocal microscopy (RCM) allowed the accurate definition of globules as junctional clusters of melanocytes protruding into dermal papillae, or widening the interpapillary space, at the edge of the lesions with a perfect correspondence to histology [7]. Consecutive confocal evaluations of MLPGs in adults supported the dynamic evolution of this process, through an eccentric elongation of junctional clusters with narrowing of their shape, associated with a centrifugal extension [7].

Recent studies have been focused on the clinical approach to MLPGs, providing further insights into MLPGs, however heterogeneous management strategies have been proposed and common practical indications are still missing [5, 8-12].

Objectives

The main aim of this manuscript is to critically review the current published data on MLPGs and to provide an integrated clinical, dermoscopic and confocal management algorithm stratified for age groups, resulting in a more appropriate and individualized management strategy.

Methods

Search Strategy

To identify eligible studies, a comprehensive search was conducted using PubMed electronic database with the following terms: “dermoscopy (MeSH)”, “dermatoscopy (MeSH)”, “confocal microscopy (MeSH), “melanocytic lesions (MeSH)”, “melanoma (MeSH)” and any one of the terms “peripheral clods (MeSH)”, “peripheral globules (MeSH)” published in English. The main search and the screening of titles and abstracts were completed independently by two reviewers (SC and LC). The manual search was concluded by the perusal of the reference sections of all relevant articles. All studies identified as relevant were analyzed and included. Case reports aiming to describe singular observations or written in non-native English language were excluded.

Results

Search Results

We completed a literature review by searching the electronic database PubMed until 1 December 2021, for all relevant records. A total of 125 articles were retrieved in the data synthesis: 120 were excluded due to being duplicated (among MeSH terms), not written in English, and not relevant (not related to melanocytic lesions). Finally, a total number of 5 studies were included and analyzed, and their main features are summarized in Table 1.

Age and Clinical Data

The impact of patient age on clinical decision-making for MLPGs is well acknowledged but different thresholds and suggestions have been proposed [5,8-11]. Williams et al...
observed all confirmed cases of melanoma (4/99, 4.0% of MLPGs) in adulthood, specifically in individuals aged 30, 35, 40 and 55, without difference in the proportion of malignancy, when dichotomizing by age 50 (5.3% vs 3.9%, p=1.0) [11]. Conversely, Ribero et al observed 9.8% of MLPGs (45/457) being melanomas (age ranged from 35 to 85 years) with a dramatic increase of frequency in patients >55 years old (10/69, 15%) [5]. Two other studies found a positive trend between histologically proven dysplastic nevi and melanoma with patients’ ages, even though without statistical significance [9,10]. In particular, Reiter et al reported a diagnosis of melanoma for 39.2% (115/293) of total MLPGs with an average age of 50 years old (range 20-85 years old), and more than half of cases (68%) being younger than 60 years old [9]. A lower percentage of melanoma (1.9%, 3/154 MLPGs) was observed by Pampín-Francoin et al with 49.5 years old estimated as the median age of malignancy in high-risk patients, defined as patients under digital dermoscopic surveillance for atypical mole syndrome and/or personal or familial history of melanoma [10]. In a similar selected population of high-risk adults, Carbone et al reported a higher rate of malignancy with 19 melanomas in 135 MLPGs (14%) with a mean age of 49.8 years old and 10% of cases occurring even in patients under 30 years old [8] (Table 1).

Concerning the anatomic site of MLPGs, the most common location was the torso and especially the back [5,8-10], while the risk of finding a melanoma when removing an MLPG resulted significantly higher in the extremities and head/neck [5,9]. A gender prevalence of MPLGs was largely not reported except for two studies with controversial results [5, 8-11]. In addition, Pampìn-Francoin et al. reported an average size of MLPGs of 4.1 mm with a significant association with the diagnosis of melanoma in lesions ≥6mm in diameter, as well as in MLPGs showing asymmetry in two axes [10]. Moreover, the authors highlighted that multiple MLPGs in a single patient were statistically less likely to be diagnosed as melanoma [10] (Table 2).

### Dermoscopy

The morphology and distribution of peripheral globules along with the presence of additional atypical features in MLPGs was recently investigated, with the objective to identify specific structures indicating a diagnosis of melanoma [8-11].

Dermoscopic findings that support a diagnosis of melanoma included atypical globules (irregular in shape, size or color) and/or their asymmetrical distribution. Completely circumferential atypical globules are reported to have the highest risk of being melanoma, followed by focal circumferential atypical globules and focal circumferential typical globules [9]. Globules distributed in more than a single rim (tiered) and departing within the edge of a lesion were found to be more frequently observed in melanoma rather than nevi, as were peripheral globules covering less than 25% of the entire circumference (especially in case of <1-history) [9,10]. In addition, the reappearance of peripheral globules after their previous disappearance has been also related to a diagnosis of melanoma, and this finding is in contrast with the expected evolution of MLPGs [2,10].

Other relevant diagnostic clues suggesting melanoma were the presence of blue-grey regression areas (especially when involving a large part of an MLPG, >50%) and atypical
Papillary dermis were seen either in benign nevi or in melanomas [10].

Proposal of an Integrated Management Algorithm

Herein we propose a flowchart algorithm for individualized management of MLPGs considering clinical, dermoscopic and confocal criteria, with the aim to identify melanomas at an early stage and to reduce as much as possible the unnecessary surgical excision of benign nevi (Figure 1). The proposed algorithm is outlined to provide risk stratification and includes the following steps:

**MLPGs in Patients <35 Years Old:**

Regular dermoscopic monitoring is recommended for lesions showing an organized rim of globules with a reticular, globular, or mixed central pattern. A decreased density of peripheral globules resulting in total disappearance, in an overall period of 4-5 years, is expected. This clinical evolution allows the interruption of follow-up surveillance at the end of the process.

We suggest performing RCM in MLPGs when at least two atypical dermoscopic structures are detected, as we still consider the very low percentage of melanoma exhibiting this pattern in patients younger than 35 years old. In the absence of cyto-architectural atypia a dermoscopic follow-up can be extended whereas in presence of confocal melanoma-specific criteria, surgical excision is recommended (Figure 1). The proposed algorithm is outlined to provide risk stratification and includes the following steps:

**MLPGs in Patients 35-55 Years Old:**

In this age group, MLPGs should be managed with more caution, with a careful assessment of dermoscopic features: if any atypical network [10]. Eccentric blotches, tan structureless peripheral areas and vascularization were also considered worrisome features [10,11]. In presence of a regular distribution of peripheral globules, at least two melanoma-specific criteria were considered indicative of malignancy by Reiter et al, while for Williams et al a single melanoma specific-structure was sufficient, although such circumstance was observed in more than half of nevi and in all melanoma cases (Table 2) [9,11].

Remarkably, the risk of an MLPG being a melanoma remains not negligible even for lesions that exhibit only peripheral regular globules without additional worrisome dermoscopic criteria [5].

Confocal Microscopy

*In-vivo* confocal evaluation of MLPGs, with a detailed analysis of global architecture and cytological aspects, was performed in two studies [8,10]. Classical melanoma-specific findings were detected in 100% of malignant MLPGs [8,10]. In detail, the presence of intraepidermal pagetoid cells (roundish or dendritic in shape) was strongly related to the diagnosis of melanoma [10]. Moreover, architectural disarray of the dermo-epidermal junction (DEJ), unspecific pattern or non-edged dermal papillae, and atypical junction thickening represented confocal findings more frequently observed in malignant lesions. Atypical cells at the DEJ, especially when multiple, along with the presence of irregular and sparse peripheral nests with an evident cleft, were also reported as being associated with histologically proven melanomas (Table 2) [8,10]. No lesions showed true cerebriform nets. Inflammatory cells and melanophages at the papillary dermis were seen either in benign nevi or in melanomas [10].

### Table 2. Clinical, dermoscopic and confocal criteria associated with the diagnosis of melanoma showing peripheral globules.

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Dermoscopy</th>
<th>RCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremities and head/neck</td>
<td>Regular PG with at least 2 melanoma-specific structures OR</td>
<td>Epidermis</td>
</tr>
<tr>
<td>Single lesion rather than multiple MLPG</td>
<td>≥2 of the following findings</td>
<td>Pagetoid cells (roundish or dendritic)</td>
</tr>
<tr>
<td>≥6 mm diameter</td>
<td>PG in less than 25% of the circumference with 1 year history</td>
<td>DEJ</td>
</tr>
<tr>
<td>Asymmetry in two axes</td>
<td>Reappearance of PG</td>
<td>Unspecific pattern</td>
</tr>
<tr>
<td></td>
<td>PG irregular in size, shape, or color</td>
<td>Non-edged dermal papillae</td>
</tr>
<tr>
<td></td>
<td>Atypical and/or asymmetric distribution of PG</td>
<td>Architectural disarrangement</td>
</tr>
<tr>
<td></td>
<td>Blue-grey regression structures involving &gt;50% of the lesion</td>
<td>Atypical thickenings</td>
</tr>
<tr>
<td></td>
<td>Vascularization</td>
<td>Atypical cells</td>
</tr>
<tr>
<td></td>
<td>Off-center blotches</td>
<td>Peripheral dense irregular</td>
</tr>
<tr>
<td></td>
<td>Peripheral tan structureless areas</td>
<td>(sparse) nests</td>
</tr>
</tbody>
</table>

RCM= reflectance confocal microscopy, MLPG= melanocytic lesions with peripheral globules, PG= peripheral globules, DEJ= dermal-epidermal junction

networks [10]. Eccentric blotches, tan structureless peripheral areas and vascularization were also considered worrisome features [10,11]. In presence of a regular distribution of peripheral globules, at least two melanoma-specific criteria were considered indicative of malignancy by Reiter et al, while for Williams et al a single melanoma specific-structure was sufficient, although such circumstance was observed in more than half of nevi and in all melanoma cases (Table 2) [9,11].
Figure 1. Our proposed algorithm for the clinical management of melanocytic lesions with peripheral globules, including dermoscopic and confocal findings in different age groups.

Figure 2. Invasive melanoma (Breslow 0.9 mm) on the upper back of a 33-years old man: dermoscopy (a), RCM (b,c) and histology (d). Irregular blotches, shiny white streaks and blue-whitish veils are observed at dermoscopy beyond a regular distribution of peripheral globules (a). A confocal section of the dermal-epidermal junction displays dendritic cells and sparse nests (blue squares) (b, low magnification; c, high magnification) corresponding to the epidermal spreading of melanocytes and discohesive nests seen on histology (d) [Haematoxylin and eosin stain, original magnification x200].
warning signal and the chance of an MLPG being a melanoma exhibiting only organized peripheral globules without other worrisome dermoscopic features represents a concrete risk after 55 years old [5].

Limitations
A limitation of this work is the inclusion of different studies with heterogeneous methodological cohorts and interventions, with no age-group standardisation. In addition, it should be considered that non-proven histologic MLPGs were not considered in the studies, and this may have contributed to a realistic underestimation of benign nevi exhibiting peripheral globules. This scenario may be due to the most common approach of favoring a surveillance program of MLPGs over time, under 35 years old in daily practice. Lastly, data synthesising dermoscopic and confocal criteria were retrieved from a small number of studies, and larger prospective datasets are needed to validate the utility of the proposed algorithm. The suggested management indications should be interpreted with caution and individualized for every single patient.

dermoscopic structure is detected, surgical excision is recommended. In addition, we suggest performing RCM evaluation also in the absence of melanoma-specific dermoscopic criteria (Figure 3). Confocal cyto-architectural irregular features require surgical excision of the lesion, while a regular follow-up is suggested in case of reassuring findings. During the follow-up period, surgery is recommended where new atypical dermoscopic criteria are observed.

The decision to perform RCM in the range of 35-55 years old, even in presence of reassuring dermoscopic criteria, is due to the still not negligible risk of a regular MLPG being a melanoma. Indeed, 50 years old was assessed as the median age of patients with a proven histological diagnosis of melanoma in different studies [9,10] and confocal evaluation has been demonstrated to disclose irregular/atypical findings with a 100% sensitivity for the diagnosis of MM [8,10].

MLPGs in Patients >55 Years Old: in this age group, the suggested management is surgical excision in all cases. While growth markers of melanocytic lesions are expected in young adults, the observation of MLPGs in the elderly represents a

Figure 3. Nevus on the right leg of a 46-year-old woman: dermoscopy (a), RCM (b,c) and histology (d). Peripheral globules are symmetrically organized at the edge of the lesion (a), corresponding to dense melanocytic nests (blue squares) located at the dermal-epidermal junction and papillary dermis upon confocal view at low (b) and high (c) magnification. A ringed pattern composed of edged dermal papillae is observed in the central area (b). Junctional melanocytic nests are observed at histopathology (d) [Haematoxylin and eosin stain, original magnification x200].
Conclusions

MLPGs are frequently seen in daily practice and represent a clinical challenge requiring the most appropriate management for individual patients. Herein we propose a multi-step and age-based management algorithm based on current published data integrating clinical, dermoscopic and confocal findings, in order to increase the early recognition of melanoma and avoid surgical excision of benign lesions.

References


Management of Infections in Psoriatic Patients Treated with Systemic Therapies: A Lesson from the Immunopathogenesis of Psoriasis

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Key words: psoriasis, infection, prevention, management, covid-19

Citation: Balato A, Scala E, Eyerich K, et al. Management Of Infections In Psoriatic Patients Treated With Systemic Therapies: A Lesson From The Immunopathogenesis Of Psoriasis. Dermatol Pract Concept. 2023;13(1):e2023016. DOI: https://doi.org/10.5826/dpc.1301a16

Accepted: May 30, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Modern treatments continue to be developed based on identifying targets within the innate and adaptive immune pathways associated with psoriasis. Whilst there is a sound biologic rationale for increased risk of infection following treatment with immunomodulators, the clinical evidence is confounded by these agents being used in patients affected with several comorbidities. In an era characterized by an ever greater and growing risk of infections, it is necessary to always be updated on this risk. In this mini-review, we will discuss recent updates in psoriasis immunopathogenesis as a rationale for systemic therapy, outline the risk of infections linked to the disease itself and systemic therapy as well, and provide an overview of the prevention and management of infections.
Introduction

In the last decade, our understanding of psoriasis pathogenesis made significant steps forward leading to the development of multiple game-changer therapies [1]. Although we can confidently say that the horizon is now a little brighter, we cannot argue that “the whole job” has been done. The advent of therapies targeting specific components of the immune response has highlighted the possible association of infections with psoriasis. Whilst there is a sound biologic rationale for increased risk of infection following treatment with immunomodulators, the clinical evidence is confounded by these agents being used in moderate-to-severe psoriasis in association with several comorbidities. In this article, we summarize the available information on the risk of infections, including the respiratory ones, linked to psoriasis and immunomodulators as well. Lastly, we provide an overview of the prevention and management of infections in psoriatic patients on immunomodulatory therapies.

Immunopathogenesis of Psoriasis: An Update

Psoriasis has been primarily defined as an autoimmune, T-cell-mediated disease with dysregulated inflammatory response that is composed of both innate and adaptive immunity [1-4]. Other factors such as environmental ones and genetic susceptibility are also involved [4,5]. Several gene loci are associated with psoriasis, such as HLA-Cw6 and PSORS1-9, providing initial evidence of a possibly (auto) immune component [6,7]. However, ~ 60 loci identified contain genes involved in the immune system at large and the interleukin (IL)-23/T helper (Th)17 pathway in particular [8,9]. IL-17A is the most studied cytokine of the psoriatic IL-23/Th17 cell pathogenic axis and is claimed to be directly responsible for the development of the psoriatic lesion [10,11]. It does not act as a single cytokine but exerts its function in a complex cytokine network which includes IL-19, IL-22, IL-23, tumor necrosis factor (TNF)-α and several IL-1 family members [12-15]. IL-17A is not exclusively produced by Th17 cells in the lesion, but possibly also by several other cells: such as γδ T cells, type 3 innate lymphoid cells (ILC3s) and invariant natural killer (iNK)T cells, and other thymus-independent cells, including mast cells and neutrophils [16-19]. Besides IL-17A, the immune-derived IL-17E, the epithelial-derived IL-17C and IL-17E, have all been shown to independently participate in psoriasisform inflammation in murine models [20-22]. Interestingly, the inhibition of the IL-17A/IL-23 axis might potentially lead to the enhancement of other IL-17 cytokine members, particularly the epithelial-derived cytokines. A better assessment of the different sources and the possible IL-17 substitute cytokines is critical to better understand the mechanism of action of the current IL-23/IL-17-targeted therapies, possibly helping to explain unwanted effects or secondary loss of efficacy.

Psoriasis and Skin Infection

Psoriatic lesions show a disturbed skin barrier function, similar to the affected skin of patients with atopic dermatitis (AD) [23-24]. This altered epidermal barrier facilitates the penetration of bacteria and viruses into the skin and should lead to an increased incidence of cutaneous infections. However, the frequency of skin infections is impressively underrepresented in patients with psoriasis [25, 26]. The main reason for this clinical observation is the specific increase in the levels of antimicrobial peptides (AMPs) and antiviral peptides (AVPs) within the epidermis of psoriatic lesions [14, 27-29]. Correspondingly, the enhancement of AMPs and AVPs in the affected skin of AD patients is only minimal and these patients often suffer from bacterial and viral skin infections. The mostly up-regulated AMPs in psoriatic skin are human β-defensin (HBD)-2, S100A7 (psoriasin) and to a lesser extent HBD-3, S100A8 (calgranulin A), S100A9 (calgranulin B), and lipocalin (LCN)-2 [27, 30-32]. The spectrum of affected microbes differs among the diverse AMPs. For example, S100A7 is primarily an E. coli-killing antimicrobial peptide, whereas HBD-3 exhibits a broad spectrum of antimicrobial activity against various Gram-negative and Gram-positive bacteria as well as fungi [33]. AMPs inhibit propagation and kill microbes through various mechanisms such as destabilization of their membrane or sequestrating metal ions [33, 34]. Most of the AMPs are constitutively expressed at low levels in keratinocytes and might be strongly up-regulated by cytokines under inflammatory conditions. The powerful inducers of AMPs in epithelial cells are IL-17 and IL-22 [31, 35]. However, the synergistic action of both cytokines is essential for the strong induction of AMPs in keratinocytes [36, 37]. In psoriatic lesions, this effect might be amplified by TNF-α, interferon (IFN)-γ, IL-19, and IL-36s [15, 37-39]. Interestingly, the joint action of IL-22 and TNF-α seems to be relevant for the maintenance of epidermal integrity during infection with Candida albicans [38]. The up-regulated AVPs in psoriatic lesions comprise OAS2, BST2 (tetherin), MX1, and ISG15 [29]. The main driver for this increase is IL-29, a member of the IL-10-IFN family of cytokines [40]. In psoriatic lesions, IL-29 is produced by Th17 cells [29]. It directly acts on keratinocytes via the transmembrane receptor complex composed of IL-28R1 and IL-10R2 and activates intracellular JAK-STAT signaling. Interestingly, IL-10R2 is also a part of the IL-22 receptor complex [41]. The AVP-inducing effect of IL-29 can be only minimally amplified by IFN-γ in keratinocytes [40]. An overview of the main psoriasis signature cytokines and their effects on infections is shown in Table 1.
Psoriasis and Respiratory Infections

Lower respiratory tract infections including pneumonia are the most frequent types of serious infections among psoriasis patients as documented by numerous registries [42, 43]. The incidence of pneumonia seems to be even increased among psoriasis patients compared to those without psoriasis [44,45]. However, it is not definitely clear to what extent this increase is related, either to psoriasis itself, its concomitant disorders, or its treatment [44]. In fact, psoriasis patients frequently suffer from diabetes mellitus, hyperlipidemia, and hypertension, are smokers, and have elevated body mass index (BMI), which can make them vulnerable to infectious diseases [25,46].

Systemic Therapies and Infection Risk, Including SARS-CoV-2

The conventional systemic therapies for plaque psoriasis include cyclosporine, methotrexate, and oral retinoids [47]. Cyclosporine is a calcineurin inhibitor broadly suppressing T cells; methotrexate, and retinoids have multiple effects on several immune cells. More recently, 2 small-molecule drugs

Table 1. Psoriasis signature cytokines and their effects on infections.

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Cellular sources</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-12</td>
<td>DCs, monocytes, macrophages, neutrophils, B cells and KCs</td>
<td>Enhances HBD-2 production in KCs, and the antimicrobial activity of macrophages</td>
</tr>
<tr>
<td>IL-17A</td>
<td>Th17 cells, ILC3s, mast cells, neutrophils, CD8+ T cells, γδ T cells, NK cells, iNKT cells, and LTi cells</td>
<td>Induces the production of AMPs (HBD-2, LL-37, LCN-2, and S100A7-9) in KCs, neutrophil recruitment, and immunity to extracellular pathogens</td>
</tr>
<tr>
<td>IL-17C</td>
<td>Prostate and fetal kidney cells, KCs, colonic epithelial cells, and lung epithelial cells</td>
<td>Enhances epithelial host defense (HBD-2/-3, and S100A7-9) in an autocrine/paracrine manner</td>
</tr>
<tr>
<td>IL-17E</td>
<td>Intraepithelial lymphocytes, lung epithelial cells, alveolar macrophages, eosinophils, basophils, NKTh2 cells, mast cells, and cells of the gastrointestinal tract and uterus</td>
<td>Promotes innate cell recruitment and activation. Provides immunity to extracellular pathogens</td>
</tr>
<tr>
<td>IL-17F</td>
<td>Th17 cells, mast cells, neutrophils, CD8+ T cells, γδ T cells, NK cells, NKT cells, and LTi cells</td>
<td>Synergistically cooperates with IL-17A and IL-22 for the induction of AMPs in KCs. Provides immunity to extracellular pathogens and is involved in neutrophil recruitment</td>
</tr>
<tr>
<td>IL-19</td>
<td>Monocytes, DCs and KCs</td>
<td>Increases the production of AMPs (S100A7-9) in KCs and amplifies IL-17A activity.</td>
</tr>
<tr>
<td>IL-21</td>
<td>Th17 cells, Th1* cells, Th2 cells, CD8+ T cells, and NKT cells</td>
<td>Enhances the antimicrobial activity of macrophages, and maintains the CD8+ T cell effector activity during the infection</td>
</tr>
<tr>
<td>IL-22</td>
<td>Th22 cells, Th17 cells, Th1 cells, CD8+ T cells, γδ T cells, ILC3s, NKT cells, LTi cells, alveolar macrophages*, and neutrophils*</td>
<td>Increases the expression of HBD-2/-3, and S100A7-9 in KCs, and reinforces TNF-α activity</td>
</tr>
<tr>
<td>IL-23</td>
<td>DCs, macrophages, and psoriatic KCs</td>
<td>Induces HBD-2 expression in KCs, and optimizes the antimicrobial activity of macrophages</td>
</tr>
<tr>
<td>IL-26</td>
<td>Th17 cells, Th1 cells, epithelial cells, NK cells, alveolar macrophages, and macrophage-like synoviocytes</td>
<td>Exerts antiviral and antimicrobial actions, as well as regulates the expression of HBD-2/-3</td>
</tr>
<tr>
<td>IL-29 (alternative name INFλ)</td>
<td>Th17 cells, DCs, macrophages, mast cells, and alveolar cells</td>
<td>Induces the production of antiviral proteins (MX1, BST2, ISG15, and OAS2) in KCs</td>
</tr>
<tr>
<td>IL-36s</td>
<td>KCs, macrophages, monocytes, DCs, and lymphocytes</td>
<td>Promote viral resistance, and the production of AMPs in KCs</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Macrophages, monocytes, DCs, NK cells, T cells, B cells, and KCs</td>
<td>Induces the production of S100A7 and HBD-2/-3, as well as antimicrobial chemokines CXCL-9/-10/-11 in KCs</td>
</tr>
</tbody>
</table>

*Controversial among researchers. AMPs antimicrobial peptides, DCs dendritic cells, ILC3s type 3 innate lymphoid cells, KCs keratinocytes, LTi lymphoid tissue inducer, iNKT invariant natural killer T cells, Th T helper. Data from multiple sources [12-15, 20-22, 29, 31, 35-41, 81-98]
have been approved for the treatment of plaque psoriasis: apremilast, an oral phosphodiesterase (PDE)-4 inhibitor, and dimethyl fumarate [48,49]. Both molecules impact the NF-kB complex and have broad functions on the immune system. Modern biological therapies, such as anti-TNF-α, anti-IL-12/23, anti-IL-17, and anti-IL-23 antibodies, are designed to block specific molecular steps important in the pathogenesis of psoriasis. Namely, anti-TNF-α agents neutralize TNF-α which has a dual role as an upstream mediator of T cell differentiation into Th1, Th17 and Th22 cells, as well as a pro-inflammatory mediator synergistic with IL-17A, IL-17F, and IL-22 [50]. The anti-IL-12/23 agent targets the p40 subunit shared by IL-12 and IL-23 preventing their interaction with the receptor and thereby blocking Th1/Th17 immunity [1,50]. This was further developed into biologics neutralizing only IL-23 via the p19 subunit, thereby only blocking Th17 immunity [1]. Finally, direct interaction with IL-17A and/or other members of the IL-17 family is a successful strategy realized through IL-17A, IL-7RA, or bispecific IL-17A/F targeting.

However, analysis of the population-based electronic medical record database from the UK on approximately 200,000 patients with psoriasis indicates that patients with moderate-to-severe disease that receive immunosuppressive therapies do have an increased risk for opportunistic infections and reactivation of varicella-zoster virus [51]. Furthermore, analyzing data from psoriasis patients treated with biologic (n=2258) or non-biologic systemic agents (n=3631) demonstrated that systemic therapies with biologics significantly increase the overall risk for serious infection [52]. The extent of impairment and the type of infection are related to the mode of action of individual drugs or drug groups [1]. For instance, TNF-α antagonists can lead to the reactivation of latent tuberculosis and IL-17 neutralization may result in mucocutaneous candidiasis [1]. However, it should be noted, there is no signal for increased risk of invasive fungal disease due to anti-IL-17 therapy [53]. Cases of opportunistic infections like atypical histoplasmosis or toxoplasmosis have been mainly reported in connection with blocking TNF-α or IL-12/IL-23 p40 [53,54]. Accordingly, the evaluation of registry data primarily notes the association of the use of infliximab, a chimeric monoclonal anti-TNF-α antibody, with increased incidence of pneumonia [44,45]. Furthermore, while neutralizing TNF-α or IL-17 has been associated with such a risk, there is no evidence that blocking IL-23 increases the risk of respiratory tract infections [55]. Despite the relevant concomitant disorders such as obesity, hypertension, and diabetes, recent data accumulated during the Covid-19 pandemic indicate that patients with psoriasis with or without systemic treatment are neither at higher risk for infection with SARS-CoV-2 nor show more severe symptoms [56]. This might be caused by the fact that cytokines, such as IL-1β and IL-6, which may play a pathogenic role in the severe/fatal course of Covid-19 infection are only moderately expressed in psoriatic lesions and do not play an important role in psoriasis pathogenesis compared to other inflammatory skin diseases [57,58]. Importantly, the incidence of Covid-19 infection, Covid-19-related hospitalization, and Covid-19-related death do not seem to be elevated among psoriasis patients treated with biologics [60,61]. The disease course in most patients with biological treatment was even milder, indicating that the anti-cytokine therapy may be beneficial in preventing a severe cytokine storm [59,62]. A schematization of the risks and benefits of cytokine-blocking therapies in psoriasis is displayed in Figure 1.

**Prevention and Management of Infections in Psoriatic Patients Treated With Systemic Therapies**

As any patient with moderate to severe psoriasis may progress to immunomodulatory therapies, it is important that their immunizations are up to date. Two general strategies have been suggested: screening for infection prior to therapy initiation as well as providing protection through vaccination. As for the first strategy, guidelines suggest tuberculosis screening before starting all biological therapies [63,64]. However, data from clinical trials and post-marketing surveillance with IL-23 and IL-17 inhibitors suggest that they are not crucial to tuberculosis reactivation [65]. Furthermore, screening for *Candida* infections, hepatitis, human immunodeficiency virus (HIV), and other chronic infections is generally recommended. As for the latter, vaccination is a proven strategy to reduce infections. In view of this, dermatologists can play an important role in educating patients about immunizations. To prevent severe infections, it is suggested that psoriatic patients receive their complete recommended vaccinations (especially live vaccines) before initiating biological therapy [66]. In short, the medical board of the National Psoriasis Foundation recommends that all patients with moderate-to-severe psoriasis have an assessment of their immunization status, including immunization or disease history for varicella zoster, *Haemophilus influenzae*, tetanus, pertussis, hepatitis A and B, human papillomavirus (HPV), influenza, *Neisseria meningitidis*, and *Streptococcus pneumoniae* during initial workup [67]. Notably, vaccines such as *Mycobacterium vaccae*, live attenuated varicella zoster virus and Leishmania amastigotes have been reported to be effective during psoriasis treatment [68-70] even though these data need to be confirmed in larger and controlled clinical trials. Lastly, vaccination against SARS-CoV-2 is recommended in patients with psoriasis, even in those under biological therapy [71].

Hence, it is clear now that immune pathways involved in psoriasis pathogenesis contribute to host defense against certain pathogens, thus a possible consequence is represented
by the fact that a selective inhibition might predispose to specific infections. Nevertheless, some biologic agents and novel small molecule drugs (i.e., apremilast) appeared to be safer or at least not associated with significant increases in the risk of serious infections, compared to conventional nonbiologic systemic compounds [72]. Mild to moderate infections (i.e., upper respiratory tract infections) or minor surgery (i.e., skin surgery, dental procedures) do not usually cause treatment discontinuation where it would otherwise be continued. Delayed starting or interruption of immunomodulatory therapies is recommended in case of clinically meaningful active infection (severe signs and symptoms requiring systemic oral or intramuscular antibiotic, antiviral, or antifungal therapy) or serious infection requiring hospitalization or intravenous antibiotic, antiviral, or antifungal therapy. Evaluating the risk-benefit ratio for recurrent serious infections, therapy can be restarted once infection has been fully resolved, empirically after 2-4 weeks from the resolution of the infectious event [73]. Analogous therapeutic management during the SARS-CoV-2 pandemic has been suggested [74,75]. In the event of SARS-CoV-2 infection, psoriasis treatments should be suspended and resumed after complete resolution of COVID-19 symptoms and SARS-CoV-2 negativization. On the contrary, in those asymptomatic SARS-CoV-2+ patients with high-need-to-treat psoriasis, as well as in psoriasis patients who have had a severe hospital course or the persistence of 1 or more symptoms of COVID-19, beyond the acute phase of the illness, the decision to restart treatment

**Figure 1.** Schematization of risks and benefits of cytokine blocking therapies in psoriasis. D dendritic cell, IL interleukin, K keratinocyte, Th T helper, TNF tumor necrosis factor.
should be taken on a case-by-case basis [76,77]. Similar to active serious infections, in case of major surgery (i.e., under general anesthesia with exposure of large body areas, internal organ surgery), guidelines recommend treatment interruption, evaluating case-by-case patient characteristics, the risk of infection, the risk of psoriasis worsening and consultation with the surgeon [78]. Therapy restart can be considered after full recovery. Nevertheless, real-life data on perioperative management are limited and do not provide strong evidence of peri- or post-operative complications due to continuous treatment with biologic agents or apremilast [78-80]. Infectious diseases to consider for selecting biological and new small-molecule therapies are listed in Table 2.

**Conclusion**

In an era characterized by an ever greater and growing risk of infections, but at the same time by increasingly specific and advanced immune-mediated therapies, it is necessary to always be updated on the risk of such infections and on the ability to manage them. Currently, we are witnessing a revolution in the treatment of psoriasis where the starting point is the translational approach, and we firmly believe that by following this path we can reach a wider knowledge that will help us in preventing and treating properly infections associated with psoriasis.

**References**

13. Carrier Y, Ma HL, Ramon HE, et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications

**Table 2. Infectious diseases to consider for selecting biological and new small-molecule therapies.**

<table>
<thead>
<tr>
<th>Class of agents</th>
<th>Drug</th>
<th>HCV</th>
<th>HBV</th>
<th>HIV</th>
<th>Latent TB</th>
<th>CMCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF-α</td>
<td>Etanercept</td>
<td>Preferred</td>
<td>Not preferred</td>
<td>Preferred</td>
<td>Not preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
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<tr>
<td></td>
<td>Infliximab</td>
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<td></td>
<td>Certolizumab</td>
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<tr>
<td></td>
<td>Golimumab</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anti-IL-12/23</td>
<td>Ustekinumab</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>Anti-IL-17A</td>
<td>Secukinumab</td>
<td>Preferred</td>
<td>Likely safe/Not enough data</td>
<td>Likely safe/Not enough data</td>
<td>Preferred</td>
<td>Not preferred</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-IL-17RA</td>
<td>Brodalumab</td>
<td>Preferred</td>
<td>Likely safe/Not enough data</td>
<td>Likely safe/Not enough data</td>
<td>Preferred</td>
<td>Not preferred</td>
</tr>
<tr>
<td>Anti-IL-23</td>
<td>Guselkumab</td>
<td>Preferred</td>
<td>Not enough data</td>
<td>Not enough data</td>
<td>Preferred</td>
<td>Not enough data</td>
</tr>
<tr>
<td></td>
<td>Tildrakizumab</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Risankizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral novel small molecule</td>
<td>Apremilast</td>
<td>Preferred</td>
<td>Not enough data</td>
<td>Not enough data</td>
<td>Preferred</td>
<td>Not enough data</td>
</tr>
</tbody>
</table>

CMCC chronic mucocutaneous candidiasis, HBV hepatitis B virus, HCV hepatitis C virus, HIV human immunodeficiency virus, IL interleukin, RA receptor A, TB tuberculosis, TNF tumor necrosis factor. Data from several sources [99-101].

**References**

Introduction: Onychomycosis represents a global burden accounting for about 50% of nail consultations. Several studies have tried to assess the dermoscopic features of onychomycosis. With the multiplication of papers, several “new” dermoscopic signs keep being added leading to some inconsistency in onychoscopic terminology.

Objective: This study aimed to summarize the existing literature on the dermoscopic features of onychomycosis and propose a unified onychoscopic terminology.

Methods: The literature search was performed using PubMed and Scopus databases up to October 30, 2021 to identify eligible contributions. In total, 33 records (2111 patients) were included.

Results: The main dermoscopic signs of onychomycosis are “ruin appearance”, “longitudinal striae” and “spikes” on the proximal margin of onycholytic areas, with a specificity of 99.38%, 83.78%, and 85.64% respectively. The “aurora borealis” sign had the highest sensitivity and specificity.

Conclusions: The current review provides a framework for issues related to the onychoscopic terminology of onychomycosis and is intended to serve as an aid for students, teachers, and researchers. We proposed a unifying terminology to describe dermoscopic signs of onychomycosis. Dermoscopic signs of onychomycosis show good specificity and are useful in distinguishing nail psoriasis, trauma, and onychomycosis. It helps differentiate fungal melanonychia from nail melanoma, nevi, and melanocytic activation.
Introduction

Onychomycosis represents all fungal infections of the nail. It is frequent, accounting for about 50% of nail consultations [1]. Onychomycosis could be due to dermatophytes (tinea unguium) as well as non-dermatophytes. Management of onychomycosis is challenging due to diagnostic difficulties, slow nail regrowth, long treatment periods, resistance to systemic medications, possible related side effects, and frequent recurrences. Direct microscopy and fungal culture are the gold standards for the diagnosis of onychomycosis. However, fungal culture has low sensitivity (35–60%) and may require several weeks [2]. Dermoscopy of the nail unit (onychoscopy) is a quick, inexpensive, and reliable tool used for the diagnosis of cutaneous tumors, inflammatory disorders, and skin infections. Several studies addressed the dermoscopic signs of onychomycosis frequently using metaphorical terminology [3]. With “new signs” being introduced (like the “sulphur nuggets” aspect) and the absence of a widely accepted consensus on the onychoscopic terminology, some degree of discrepancy among the definitions of the dermoscopic signs of onychomycosis exists (Table 1).

Dermoscopy can help differentiate onychomycosis from similar conditions including nail psoriasis and traumatic nail dystrophy [3] and can be used to characterize fungal melanonychia [4–7]. However, the sensitivity and specificity of the dermoscopic signs of onychomycosis are yet to be determined.

The aim of this study was to summarize the existing literature on the dermoscopic features of onychomycosis and its diagnostic value and propose a unified onychoscopic terminology.

Methods

This literature search was performed using PubMed and Scopus databases (from the databases’ inception up to October 30, 2021) to identify eligible contributions. The following search strategy was used: (“onychomycosis” OR “Tinea unguium” OR “nail fungal infection”) AND (“onychoscopy” OR “dermatoscopy” OR “Dermoscopy” OR “videodermatoscopy” OR “videodermoscopy”).

Two dermatologists (N.L. and E.M.) independently screened titles and abstracts for eligibility. Only papers in the English language were considered for inclusion. Editorials, commentary, and review articles were excluded. All contributions reporting one or multiple cases of onychomycosis and describing its dermoscopic features were included. Reference lists of included articles were further screened for additional eligible publications. Any discrepancy between the 2 authors (N.L. and E.M.) was resolved by consensus. Each eligible article was retrieved in full, and the epidemiological, mycological, dermoscopic, and histopathological data were extracted.

Both descriptive and analytical statistics were performed. The dermoscopic features of onychomycosis were first analyzed based on the initial description by the authors of included articles (Table 2). Then the following terms that share the same definition: “jagged edge with spikes”, “spiked pattern” and “intermittent spiked pattern” were grouped as “spikes” for analytical statistics.

Chi-squared test, when applicable, or Fischer exact test, were used to examine differences in categorical variables. The sensitivity and specificity of the most frequently reported dermoscopic features of onychomycosis were calculated. A P-value lower than 0.05 was considered significant.

Results

The literature search yielded 180 records. Of the 110 papers examined after duplicate removal, 36 were review articles, and 32 were not relevant. Overall, 5 contributions were not in the English language, and 7 did not include information regarding the frequency of dermoscopic signs of onychomycosis. Consequently, 33 records were included in this review [2,3,12–21,4,22–31,5,32–34,6–11]. The process of selecting relevant articles is illustrated in Figure 1.

In total, 2048 patients with onychomycosis were included. The clinical classification of onychomycosis is divided into 6 patterns based on the point of fungal entry into the nail unit. The clinical classification of onychomycosis was specified in 1885 cases:

- Distal/lateral subungual onychomycosis (DLSO): 1514, 71.7%
- Superficial onychomycosis (SO): 31, 1.6%
- Proximal subungual onychomycosis (PSO): 21, 1.1%
- Total dystrophic onychomycosis (TDO): 266, 14.1%
- Mixed pattern (MO): 51, 2.7%
- Endonyx onychomycosis: 2 cases

Methods to diagnose onychomycosis were described in 27 of the included papers. The diagnosis was based on KOH examination [4,7,11,16,17,23,27–32,35], fungal culture [2,3,5,8,13,16,19,20,24,25,33,34], and/or histologic examination of nail plates [5,8,10,19,20,24].

The dermoscopic features of onychomycosis are summarized in Table 2. The most common onychoscopic signs were:

- Distal/lateral subungual onychomycosis (DLSO):
  - Ruin Appearance

Ruin Appearance

Ruin appearance refers to the distal part of the thickened nail plate showing ventral indentations caused by dermal
### Table 1. Definitions.

<table>
<thead>
<tr>
<th>Dermoscopic features</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruin appearance</td>
<td>Ventral indentations of the nail plate caused by dermal debris. Some authors consider that <em>ruin appearance and subungual hyperkeratosis are the same sign</em>(^{19,32}), while others defined <em>ruin appearance as a distal irregular termination at the edge of the nail plate</em>(^{30}).</td>
</tr>
<tr>
<td>Subungual hyperkeratosis</td>
<td>Hyperkeratosis of the subungual area under the distal margin of the nail plate(^{4})</td>
</tr>
<tr>
<td>Sulphur nuggets</td>
<td>Described for the first time by Leeyaphan et al. as yellow clumping sulfur nugget-like debris under the nail plate.(^{8})</td>
</tr>
<tr>
<td>Longitudinal striae</td>
<td>Longitudinal pigmentation of different colors in streaks within the nail plate</td>
</tr>
<tr>
<td>onycholysis</td>
<td>Separation of the nail plate from the nail bed</td>
</tr>
<tr>
<td>Jagged edge with spikes/</td>
<td>A nonlinear border at the proximal edge of an onycholysis area, with a sharp white longitudinal indentation pointing to the proximal nail fold</td>
</tr>
<tr>
<td>spiked pattern</td>
<td></td>
</tr>
<tr>
<td>Straight onycholytic edge</td>
<td>A linear edge of the proximal margin of an onycholytic area without indentations</td>
</tr>
<tr>
<td>Distal irregular termination</td>
<td>Refers to the distal pulverization of the nail plate(^{17,32,29})</td>
</tr>
<tr>
<td>Splinter hemorrhage</td>
<td>Longitudinal brown, black, or purple linear hemorrhages(^{30})</td>
</tr>
<tr>
<td>Chromonychia</td>
<td>Multicolored, black, brown, white or yellow pigmentation of the nail plate.</td>
</tr>
<tr>
<td>Aurea borealis</td>
<td>Area of various colors associating various degrees of green, bluish-gray, black, white, and yellow in association with onycholysis, striae and streaks.(^{11}) Some authors consider “jagged edge with spikes” sign to be equivalent to “aurora borealis” pattern.(^{29})</td>
</tr>
<tr>
<td>Leukonychia</td>
<td>True leukonychia A white discoloration throughout the entire thickness of the nail plate, responsible for the opaque appearance</td>
</tr>
<tr>
<td>Pseudo leukonychia</td>
<td>Seen in white superficial onychomycosis (SO), where only the superficial surface of the nail plate is invaded.(^{29})</td>
</tr>
<tr>
<td>Homogeneous leukonychia</td>
<td>Homogenous white opacity of the nail plate, greater than 1 mm in size.(^{19,20})</td>
</tr>
<tr>
<td>Punctate leukonychia</td>
<td>White globules with dimensions of less than 1 mm on the nail plate(^{19})</td>
</tr>
<tr>
<td>Longitudinal leukonychia</td>
<td>White parallel lines in the nail plate</td>
</tr>
<tr>
<td>Transverse leukonychia</td>
<td>Horizontal white striae in the nail plate</td>
</tr>
<tr>
<td>Grid pattern</td>
<td>Seen in superficial onychomycosis (SO). The grid pattern is the result of the intersection of longitudinal and transverse leukonychia.(^{10})</td>
</tr>
<tr>
<td>Melanonychia</td>
<td>Longitudinal melanonychia A longitudinal band extending from the proximal nail fold to the distal free edge of the nail plate</td>
</tr>
<tr>
<td>Non-longitudinal homogenous pattern</td>
<td>Structureless pigmentation of the nail plate</td>
</tr>
<tr>
<td>Reverse triangular pattern</td>
<td>Nail pigmentation that is wider at the distal end compared to the proximal part of the nail plate</td>
</tr>
<tr>
<td>Triangular sign</td>
<td>Nail pigmentation is wider at the proximal area compared to the distal end of the nail plate</td>
</tr>
<tr>
<td>Micro Hutchinson</td>
<td>Cuticular pigmentation that is normally invisible to the naked eye</td>
</tr>
<tr>
<td>Hutchinson sign</td>
<td>Nailfold or hyponychium pigmentation</td>
</tr>
<tr>
<td>Pseudo-Hutchinson sign</td>
<td>Nail matrix pigmentation detected through a relatively translucent cuticle at the proximal nail fold.(^{4})</td>
</tr>
</tbody>
</table>
The frequency of linear edge in OM varied between 2% and 22% (a mean of 8%) and it is thought to be secondary to trauma preceding OM [36].

Spikes

“Spiked pattern”, “intermittent spiked pattern” and “Jagged edge with spikes” share the same definition. It is characterized as indentations at the proximal edge of the onycholytic area (Figure 2c) [23]. These structures correspond to the distal-to-proximal invasion of the nail bed’s longitudinal ridges by dermatophytes [3,11,23]. The frequency of jagged edges with spikes varied between 39% and 100% (a mean of 58%) [3,5–9,12–15,17–21,24,29–34,36]. These structures were significantly associated with DLSO, very frequent in TDO, and never described in SO, PSO and endonyx onychomycosis (Table 3).

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Spikes can also be seen in onychorrhexis, but are located in the proximal part of the nail [11,26]. Spikes help differentiate onycholysis related to trauma and onychomycosis. The former is virtually never associated with spikes.

Chromonychia

Chromonychia is defined as a discoloration of the nail plate. It may be secondary to colony formation, flakes, or subungual debris [15,23,26]. The colors ranged from white (leukonychia), green, yellow, brown, gray, and black. The prevalence of chromonychia varies between 22 and 100%.

Table 2. Summary of the dermoscopic features of onychomycosis.

<table>
<thead>
<tr>
<th>Dermoscopic features</th>
<th>N, percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruin appearance</td>
<td>752, 68%</td>
</tr>
<tr>
<td>Longitudinal striae</td>
<td>1351, 64.9%</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>252, 65.3%</td>
</tr>
<tr>
<td>Jagged edge with spikes/spiked pattern</td>
<td>740, 58% / 516, 57.3%</td>
</tr>
<tr>
<td>Straight onycholytic edge</td>
<td>55, 8.2%</td>
</tr>
<tr>
<td>Distal irregular termination</td>
<td>340, 36%</td>
</tr>
<tr>
<td>Splinter hemorrhage</td>
<td>26, 5.3%</td>
</tr>
<tr>
<td>Chromonychia</td>
<td>531, 70.4%</td>
</tr>
<tr>
<td>Homogeneous leukonychia</td>
<td>120, 33.4%</td>
</tr>
<tr>
<td>Punctate leukonychia</td>
<td>113, 75.8%</td>
</tr>
<tr>
<td>Transverse leukonychia</td>
<td>18, 10.4%</td>
</tr>
<tr>
<td>Leukonychia (unspecified pattern)</td>
<td>182, 31.8%</td>
</tr>
<tr>
<td>Black discoloration</td>
<td>212, 23.9%</td>
</tr>
<tr>
<td>Brown discoloration</td>
<td>268, 36.9%</td>
</tr>
<tr>
<td>Yellow discoloration</td>
<td>365, 57%</td>
</tr>
<tr>
<td>Orange discoloration</td>
<td>69, 19.5%</td>
</tr>
<tr>
<td>Gray discoloration</td>
<td>29, 11.6%</td>
</tr>
<tr>
<td>Green discoloration</td>
<td>92, 40.8%</td>
</tr>
</tbody>
</table>

N: number of reported cases
Leukonychia: Leukonychia is a white coloration of the nail. It is explained by the fungal growth in the nail plate, similar to the growth in the culture medium [19]. It can be punctate, transverse (Figure 2d), or homogenous (Table 1). The frequency of leukonychia varies between 2% and 75% (a mean of 37%) [2,6,19,20,29]. Leukonychia was significantly associated with SO (p<0.001).
Fungal Melanonychia

Fungal melanonychia is a dark pigmentation of the nail plate. It is explained by the synthesis of melanin by some fungi. The best-characterized fungal melanin is 1,8-dihydroxynaphthalene (DHN) melanin. Its biosynthetic pathway is called the pentaketide pathway. The name “Pentaketide” derives from the fact that the naphthalene ring structure, that underlies the DHN-melanin pathway is formed by the binding and cyclization of five subunits of a ketone compound derived from five acetate molecules. Fungal melanin protects the fungus from the aggressions of the environment [37].

Dermoscopy helps distinguish fungal melanonychia from nail melanoma, nail matrix nevus, and melanocytic activation [4,5,7,9]. Yellow and red discoloration are significantly associated with fungal melanonychia, while the triangular sign and Hutchinson sign are features of nail melanoma and never described in association with onychomycosis (Table 4). Conversely, distal linear and reverse triangular patterns are signs of fungal melanonychia (Table 4). Indeed, in fungal melanonychia, the pigmentation is wider at the distal portion of the nail due to the distal-to-proximal progression of fungi which is responsible for the reverse triangular pattern (Figure 1). However, in nail melanomas, the pigmentation is wider in the proximal portion, resulting in a triangular melanonychia [30].

Splinter Hemorrhage

Splinter hemorrhages are linear hemorrhages caused by bleeding capillaries [16]. It is a common yet nonspecific sign of onychomycosis. It is reported in association with trauma and psoriasis [25]. The prevalence of splinter hemorrhage in onychomycosis varies between 2% and 25% (a mean of 5%) [11,17,19,21,34,36].

Sensitivity and Specificity of the Dermoscopic Signs of Onychomycosis:

Several studies compared the dermoscopic features of onychomycosis, psoriasis, and traumatic nail dystrophy [3,8,11,12,25]. The sensitivity and specificity of the dermoscopic signs of onychomycosis are summarized in Table 5. Overall the sensitivity of “ruin appearance”, “longitudinal striae”, and “spikes” are low with good specificity (Table 5). The “Aurora borealis” sign showed the highest sensitivity and specificity. Some dermoscopic signs were only
Table 3. Dermoscopic aspects and their association with clinical subtypes of onychomycosis.

<table>
<thead>
<tr>
<th></th>
<th>DLSO</th>
<th>SO</th>
<th>PSO</th>
<th>MO</th>
<th>TDO</th>
<th>Onychomycosis endonyx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruin appearance</td>
<td>142/206 0.016</td>
<td>0/5 0.001</td>
<td>1/4 NS</td>
<td>-</td>
<td>53/55 NS</td>
<td>0 NS</td>
</tr>
<tr>
<td>Longitudinal striae</td>
<td>326/496 NS</td>
<td>2/13 0.001</td>
<td>3/11 0.03</td>
<td>20/47 -</td>
<td>117/210 NS</td>
<td>2/2 NS</td>
</tr>
<tr>
<td>Spikes (Jagged edge with spikes/Spiked pattern)</td>
<td>403/657 0.002</td>
<td>4/21 NS</td>
<td>2/18 0.029</td>
<td>34/94 NS</td>
<td>95/259 NS</td>
<td>0/2 NS</td>
</tr>
<tr>
<td>Distal irregular termination</td>
<td>154/462 NS</td>
<td>1/12 0.017</td>
<td>5/10 NS</td>
<td>14/47 NS</td>
<td>126/186 NS</td>
<td>0/2 NS</td>
</tr>
<tr>
<td>Leukonychia</td>
<td>56/256 0.017</td>
<td>7/7 0.0001</td>
<td>1/7 NS</td>
<td>34/47 NS</td>
<td>0/58 NS</td>
<td>2/2 NS</td>
</tr>
</tbody>
</table>

DLSO: Distal/lateral subungual onychomycosis; MO: Mixed pattern; NS: non-significant; PSO: Proximal subungual onychomycosis (PSO); SO: Superficial onychomycosis; TDO: Total dystrophic onychomycosis;
Figure 3. “Aurora borealis” sign. Chromonychia of multiple colors, associated with onycholysis, spikes and longitudinal striae.

Table 4. Characteristics of melanonychia in patients with onychomycosis, nail matrix naevus, melanoma, and melanocytic activation.

<table>
<thead>
<tr>
<th></th>
<th>Fungal melanonychia</th>
<th>Nail matrix naevus</th>
<th>Malignant melanoma</th>
<th>Melanocytic activation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>color</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>black</td>
<td>35/128</td>
<td>12/27</td>
<td>16/25</td>
<td>0/24</td>
<td>0.16</td>
</tr>
<tr>
<td>dark brown</td>
<td>46/128</td>
<td>12/27</td>
<td>17/25</td>
<td>0/24</td>
<td>0.76</td>
</tr>
<tr>
<td>light brown</td>
<td>32/86</td>
<td>16/27</td>
<td>7/25</td>
<td>5/24</td>
<td>1</td>
</tr>
<tr>
<td>yellow</td>
<td>27/86</td>
<td>3/27</td>
<td>3/25</td>
<td>2/24</td>
<td>0.0001</td>
</tr>
<tr>
<td>grey</td>
<td>24/148</td>
<td>0/27</td>
<td>7/25</td>
<td>20/24</td>
<td>0.002</td>
</tr>
<tr>
<td>red</td>
<td>12/58</td>
<td>0/27</td>
<td>1/25</td>
<td>0/24</td>
<td>0.0001</td>
</tr>
<tr>
<td>multicolored</td>
<td>49/100</td>
<td>13/27</td>
<td>22/25</td>
<td>4/24</td>
<td>0.87</td>
</tr>
<tr>
<td>clumped/granular black</td>
<td>23/62</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>pigmentation pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>longitudinal pattern</td>
<td>57/148</td>
<td>26/27</td>
<td>17/25</td>
<td>24/24</td>
<td>1</td>
</tr>
<tr>
<td>distal diffuse pattern</td>
<td>20/88</td>
<td>-</td>
<td>6/14</td>
<td>-</td>
<td>0.18</td>
</tr>
<tr>
<td>proximal diffuse pattern</td>
<td>7/88</td>
<td>-</td>
<td>2/14</td>
<td>-</td>
<td>0.60</td>
</tr>
<tr>
<td>distal linear pattern</td>
<td>7/88</td>
<td>-</td>
<td>0/14</td>
<td>-</td>
<td>0.58</td>
</tr>
<tr>
<td>total diffuse pattern</td>
<td>21/88</td>
<td>-</td>
<td>5/14</td>
<td>-</td>
<td>0.33</td>
</tr>
<tr>
<td>reverse triangular pattern</td>
<td>19/58</td>
<td>0/27</td>
<td>1/25</td>
<td>0/24</td>
<td>1</td>
</tr>
<tr>
<td>triangular sign</td>
<td>0/86</td>
<td>3/27</td>
<td>9/25</td>
<td>0/24</td>
<td>-</td>
</tr>
<tr>
<td>Hutchinson sign</td>
<td>0/106</td>
<td>1/27</td>
<td>16/25</td>
<td>0/24</td>
<td>-</td>
</tr>
<tr>
<td>pseudo Hutchinson sign</td>
<td>3/106</td>
<td>10/27</td>
<td>15/25</td>
<td>2/24</td>
<td>1</td>
</tr>
<tr>
<td>superficial transverse striation</td>
<td>18/62</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

reported in association with psoriasis including red dots in the hyponychium and lateral folds, proximal erythematous rim of onycholytic areas, and salmon patches, while plain non-erythematous edges of onycholytic areas are only described in association with trauma.

Discussion

This is the first systematic review addressing the dermoscopic features of onychomycosis. The main dermoscopic signs of onychomycosis are “ruin appearance”, “longitudinal striae” and “spikes” on the proximal margin of onycholytic areas, with a specificity of 99.38%, 83.78%, and 85.64% respectively. The “aurora borealis” sign had the highest sensitivity and specificity.

Dermoscopy improves the diagnostic accuracy for cutaneous lesions in comparison with the naked eye examination [38]. Since the first description [3], several studies tried to assess the dermoscopic features of onychomycosis. With the multiplication of papers, and the inexistence of a widely adopted international consensus on onychoscopy similar to those related to cutaneous lesions [38], several “new” dermoscopic signs keep being added [8]. This results in some inconsistency between authors on the terminology to be used to describe dermoscopic features of onychomycosis (Table 1).
while metaphorical terminology is memorable but incomprehensible outside its context [38]. We suggest the following terminology for the most prevalent onychoscopic signs of onychomycosis:

- “ruin appearance” (metaphoric) = subungual hyperkeratosis with distal irregular termination (descriptive)
- “longitudinal striae” (descriptive)
- “spikes” (metaphoric) to replace “spiky pattern”, “Jagged edge with spikes” and “spiked pattern”

Following the third consensus conference of the International Society of Dermoscopy, standardization of terminology in dermoscopy of cutaneous lesions was adopted [38]. Both descriptive and metaphorical terminology was considered acceptable for clinical use and research [38]. Similarly, we believe that both descriptive and analytical terminology can be used to describe dermoscopic signs of onychomycosis. Descriptive (analytical) terminology has the advantage of being comprehensible and suitable for learning, and the disadvantage of possible long descriptive complex structures, while metaphorical terminology is memorable but incomprehensible outside its context [38]. We suggest the following terminology for the most prevalent onychoscopic signs of onychomycosis:

- “ruin appearance” (metaphoric) = subungual hyperkeratosis with distal irregular termination (descriptive)
- “longitudinal striae” (descriptive)
- “spikes” (metaphoric) to replace “spiky pattern”, “Jagged edge with spikes” and “spiked pattern”

**Table 5. Sensitivity and specificity of the dermoscopic signs of onychomycosis.**

<table>
<thead>
<tr>
<th></th>
<th>Onychomycosis</th>
<th>Trauma</th>
<th>Psoriasis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spikes</td>
<td>141/211</td>
<td>24/147</td>
<td>0/41</td>
<td>66.82</td>
<td>85.64</td>
</tr>
<tr>
<td>Longitudinal striae</td>
<td>76/191</td>
<td>24/142</td>
<td>0/6</td>
<td>39.79</td>
<td>83.78</td>
</tr>
<tr>
<td>Subungual hemorrhage</td>
<td>17/137</td>
<td>18/120</td>
<td>-</td>
<td>12.41</td>
<td>85</td>
</tr>
<tr>
<td>Splinter hemorrhage</td>
<td>6/147</td>
<td>11/96</td>
<td>23/41</td>
<td>4.08</td>
<td>75.18</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>31/154</td>
<td>42/129</td>
<td>6/6</td>
<td>20.13</td>
<td>61.9</td>
</tr>
<tr>
<td>Ruin appearance</td>
<td>28/157</td>
<td>1/125</td>
<td>0/35</td>
<td>17.83</td>
<td>99.38</td>
</tr>
<tr>
<td>Red dots in hyponychium</td>
<td>0/20</td>
<td>0/5</td>
<td>26/35</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Red dots in lateral folds</td>
<td>0/20</td>
<td>0/5</td>
<td>24/35</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Proximal erythematous rim</td>
<td>0/37</td>
<td>0/14</td>
<td>26/41</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Plain edges without erythma</td>
<td>0/74</td>
<td>26/27</td>
<td>0/41</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Deep pits and dots</td>
<td>24/74</td>
<td>9/27</td>
<td>14/41</td>
<td>32.43</td>
<td>66.18</td>
</tr>
<tr>
<td>Salmon patch</td>
<td>0/20</td>
<td>0/5</td>
<td>9/35</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Subungual hyperkeratosis</td>
<td>5/20</td>
<td>0/5</td>
<td>17/35</td>
<td>25</td>
<td>57.5</td>
</tr>
<tr>
<td>Aurora borealis</td>
<td>17/20</td>
<td>0/5</td>
<td>0/35</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

* the sign was only described in patients with psoriasis ** the sign was only described in association with trauma
• chromonychia (descriptive): nail discoloration
• leukonychia (descriptive): white discoloration of the nail plate

We also suggest that the pigmentation patterns described in Table 4 should be used as-is since these patterns are widely used in onychoscopic terminology and there are no related discrepancies between published articles [3–5,7].

Dermoscopy is very useful in diagnosing pigmented nails. Chromonychia is very frequent in onychomycosis with yellow and red discoloration being significantly associated with fungal melanonychia. Other signs help distinguish fungal melanonychia from nail melanoma including distal linear and reverse triangular patterns. Conversely, the triangular pattern and Hutchinson sign are features of nail melanoma [4–7,9].

In conclusion, dermoscopy is useful in diagnosing onychomycosis. The current review provides a framework for issues related to onychoscopic terminology of onychomycosis and is intended to serve as an aid for students, teachers, and researchers. Dermoscopic signs of onychomycosis show good specificity and are useful in distinguishing nail psoriasis, trauma, and onychomycosis. It helps differentiate fungal melanonychia from nail melanoma, nevi, and melanocytic activation and allows precise monitoring of nail regrowth after systemic antifungal treatment initiation (Figure 5).

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Virtual Resident Education with the Dermatologic Society of Greater New York During the COVID-19 Pandemic

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Accepted: May 2, 2022; Published: January 2023
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Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
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Technology has grown exponentially in this past decade, with a plethora of virtual communities for socializing, emotional support, online purchases, but few opportunities for virtual medical education [1]. Prior to the COVID-19 pandemic, dermatology Continuing Medical Education opportunities for both residents and board-certified dermatologists had been predominantly in-person experiences, limited to those with the time and means to attend these events. Conferences for major dermatology organizations had always been held in-person until recently. Many residents were previously unable to attend educational conferences due to limited academic time, clinical coverage, and cost. However, due to COVID-19, many groups, including the Dermatologic Society of Greater New York (DSGNY), have been forced to adapt to the changing landscape.

The COVID-19 pandemic has resulted in far-reaching changes in resident education. In a survey-based study, 60% of dermatology residents reported that COVID-19 had negatively impacted their education, with cancelled or postponed lectures and reduced patient volume in clinic [2]. In a survey-based study performed during the pandemic, 80% of residents reported high levels of anxiety regarding the American Board of Dermatology (ABD) certification examination and employment opportunities [3]. On the other hand, in a nationwide survey-based study, 99% of dermatology residents reported that virtual didactics were beneficial during the peak of the pandemic in April 2020 [4]. Thus, COVID-19 has brought about a unique opportunity to dramatically transform resident education and the DSGNY was one of the first dermatology societies to embrace that change.

Dermatopathology education may pose the greatest obstacle to remote learning. Prior to the pandemic, residents typically learned at the microscope by observing dermatopathology signouts [3]. However, with many residents having
limited rotations in dermatopathology, there have been significant disruptions due to the pandemic. In 2020, the ABD changed the testing format from utilizing microscopic slides to digital slides for the dermatopathology component on the boards. Since residents had been traditionally taught at the microscope, many residents felt unprepared for digital dermatopathology. In spring 2020, DSGNY was one of the first organizations to create a free recurring dermatopathology resident education series with Dr. Jason Cohen, a dermatopathologist at Dermpath Diagnostics in White Plains, New York. During each session, Dr. Cohen reviewed 15 unknown slides with residents in an interactive format and reinforced a methodical and algorithmic approach to approaching dermatopathology slides. The group regularly reviewed high-yield diagnoses including benign adnexal neoplasms, acantholytic disorders, autoimmune blistering disease, and infections. Residents asked for clarification on specific histologic findings or differentiating specific diagnoses either verbally or via chat. The residents who participated found these lectures incredibly helpful for their overall education and dermatopathology board review. Over 90 residents have participated thus far. We do not know the impact of this series on board pass rates or promoting dermatology residents’ interests in pursuing dermatopathology, and these topics merit further study.

Our DSGNY dermatopathology series highlights the benefits of virtual education. Residents with limited dermatopathology didactics at their own residency programs or who wanted additional training could participate in these sessions free of cost, which is helpful on a tight resident budget. Furthermore, residents who are less comfortable asking questions in real-time may feel more comfortable doing so via a virtual platform. Our lecture series is scheduled weekly to monthly and thus shorter lectures may help to circumvent mental fatigue sometimes experienced at lengthy in-person conferences. Residents with children who struggle with childcare are able to attend these lectures from home. Our virtual dermatopathology didactics are now expanding to include additional speakers, facilitating new teaching opportunities for dermatologists not directly tied to academic institutions, and giving residents different perspectives.

These lecture series are open to dermatology residents from across the United States, allowing for a unique opportunity for interactions among residents from different programs and opening the door for collaborations. Residents can learn from others’ experiences and questions during teaching sessions. Residents may utilize these virtual sessions as a platform for communication and inform one another of additional teaching sessions or grand rounds at their home institutions. These interactions may pave the way for cross-institutional research collaborations and dissemination of the newest findings in dermatology relevant to clinical care. It is also interesting to note that this may help residents pick up different approaches to dermatologic differential diagnosis, and gain exposure to approaching different patient populations from those which they are already familiar with.

However, virtual learning does raise concerns about the negative implications of limited human contact. The practice of dermatology is highly team-based, and collegiality is an essential aspect of dermatology education and patient care. Virtual learning experiences make it more difficult to have exchanges about shared patient experiences. While social distancing is necessary, we recommend that virtual networking events have small group breakouts. We are also promoting virtual one-on-one mentorship experiences between residents and attending dermatologists which will transition to in-person meetings when the time permits. Thus, residents who have had limited mentoring opportunities may be able to find a mentor through our structured program. Virtual dermatology education does raise privacy concerns as care must be taken to utilize online platforms that prohibit downloading of patient photos.

The DSGNY has played an important role in promoting resident education during this pandemic. We will continue our virtual education series for New York City dermatology residents and encourage residents from across the country to attend. We hope that this model and spirit of service may lead to similar programs nationwide, all in the interest of improving dermatology resident education.

References

Localized Vitiligo and Post-Inflammatory Hypopigmentation at the Injection Site of a COVID-19 mRNA Vaccine

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Key words: vitiligo, COVID-19, SARS-CoV2, mRNA, vaccine, BNT162b2


Accepted: May 2, 2022; Published: January 2023

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

The COVID-19 pandemic has been a global emergency since January 2020. One of the most commonly used COVID-19 mRNA vaccines is Pfizer- BioNTech vaccine BNT162b2 [1]. In a registry-based study of 414 cutaneous reactions to mRNA COVID-19 vaccines, delayed and immediate injection site reactions were the most common [2]. Herein, we discuss two similar cutaneous reactions following COVID mRNA vaccination in order to further characterize dermatologic reactions.

Case Presentation

Case 1. A 38-year-old woman, Fitzpatrick type III, presented to our consultation after the second dose of Pfizer vaccine BNT162b2. After vaccine administration, the patient described an immediate local reaction on the injection site characterized by an erythematous and edematous plaque. This reaction evolved to a hypopigmented patch with irregular borders measuring 20 mm (Figure 1A). Wood lamp examination of the lesion (Figure 1B) revealed neither fluorescence nor accentuation, which is consistent with post-inflammatory hypopigmentation. This cutaneous lesion faded after 2 months without treatment.

Case 2. A 30-year-old woman, Fitzpatrick type V, presented to our consultation after the first dose of Pfizer vaccine. Few hours after the vaccine, the patient noted an immediate local reaction characterized by an erythematous and edematous plaque with a central blister. Over two weeks, this reaction evolved to a hypopigmented patch with 25 mm of diameter and irregular borders, surrounded by...
another patch with two shades of brown (Figure 1, C-E). Wood lamp examination demonstrated a sharply demarcated bright blue-white fluorescence (Figure 1F), consistent with vitiligo. Skin biopsy was also compatible with vitiligo (Figure 2) revealing a decrease or absence of melanin pigment in lesional skin with H&E and Masson-Fontana stains, respectively. Autoimmunity laboratory study (ANAs, ANA screening, anti-dsDNA, anti-thyroid antibodies) was negative and SARS-CoV2 anti-spike antibody titers were positive of (50.8 AU/mL). She was treated with topical tacrolimus twice daily with poor response. After the second dose of the vaccine, two months later, she had no skin reaction. At four months of follow-up only the vitiligo lesion remains, the brown patch is fading away.

Conclusions

Post-inflammatory hypopigmentation is an acquired partial or total loss of skin pigmentation occurring after cutaneous inflammation. There is limited information about the mechanism and pathogenesis. Melanogenesis is a complex process. It is controlled by multiple mediators (eg, growth factors, cytokines) acting on melanocytes, keratinocytes and fibroblasts. Through the release of these mediators, cutaneous
inflammation may cause aberration of melanogenesis leading to loss of melanocytes [3]. In Case 1, inflammation resulted in hypopigmented patches at the injection site. The hypopigmentation improved overtime after the inflammation ceased.

Vitiligo is an autoimmune disease. Cytotoxic CD8+ T cells are responsible for the destruction of melanocytes. The potential for vaccines to act as triggers of autoimmune reactions is well known [4,5]. The pathophysiology underlying the relationship between SARS-CoV-2 vaccination and vitiligo remains unclear.

mRNA vaccines encoding the SARS-CoV-2 spike protein encapsulated in lipid nanoparticles gain entry into dendritic cells (DCs) at the injection site. In addition, innate sensors are triggered resulting in production of type I interferon and multiple pro-inflammatory cytokines and chemokines. In particular, vaccine-driven production of type I interferon (IFN-1) promotes differentiation of CD4+ and CD8+ effector T cells producing inflammatory and cytotoxic mediators, and CD4+ T follicular helper cells, which promote B cell differentiation into antibody-secreting plasma cells [6].

In the pathogenesis of vitiligo, both IFN-1 and DCs were demonstrated to play a significant role. The activation of DCs and the release of IFN-1 seem to be key events in vitiligo following COVID-19 vaccination. Additionally, nonspecific activation of autoreactive CD8+/CD4+ T and B cells could stimulate the immune system to produce antibodies against SARS-CoV2 spike protein and incidentally against melanocytes [7-9].

On the other hand, studies with anti-melanoma vaccines demonstrated that vitiligo observed around the injection site does not occur unless autoreactive T cells are recruited into the skin by inflammatory stimuli, suggesting that vitiligo can be initiated by some form of trauma to the skin [10].

To date, there are only five reported cases of new-onset vitiligo following COVID-19 mRNA vaccine (Table 1). In case 1, the hypopigmented patch was a result of an inflammatory response that can occur in any patient and should be differentiated from vitiligo. Case 2 is the first report of site injection site vitiligo after an mRNA vaccine. Vaccines generate an immune response which can be a trigger to develop

Figure 2. Vitiligo, Case 2. Skin biopsy performed on the edge of the hypopigmented patch. (A) Basal epidermal hyperpigmentation explained by the patient phototype. Scarce inflammatory infiltrate in the superficial dermis (H&E stain, magnification x100). (B) Slight Decrease in melanin pigment in lesional skin (H&E stain, magnification x400). (C,D) Masson-Fontana stain highlights loss of melanin on the left side of the biopsy (Fontana-Masson stain, magnification x100 and x400).
vitiligo. We can hypothesize that in case 2, autoreactive T cells responses triggered by a local injection site inflammation along with activation of DCs and the release of IFN-1 might be responsible for the development of vaccine-induced vitiligo at injection site.

References


Table 1. Literature review: reported cases of new-onset vitiligo following COVID-19 mRNA vaccine.

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Age (years)</th>
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<td>61</td>
<td>Female</td>
<td>mRNA-1273 (Moderna)</td>
<td>Face, neck, chest, abdomen</td>
<td>Several days after 1st dose</td>
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<tr>
<td>Ciccarese G [9] 2022</td>
<td>33</td>
<td>Female</td>
<td>Pfizer-BioNTech BNT162b2</td>
<td>Trunk, neck, back</td>
<td>1 week after 1st dose</td>
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<td>Militello et al. [5] 2022</td>
<td>67</td>
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<td>mRNA-1273 (Moderna)</td>
<td>Hands</td>
<td>2 weeks after the vaccine</td>
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<tr>
<td>Uğurer E et al. [8] 2022</td>
<td>47</td>
<td>Male</td>
<td>Pfizer-BioNTech BNT162b2</td>
<td>Axilla, forearms</td>
<td>1 week after 1st dose</td>
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Dermoscopy of Annular Atrophic Lichen Planus on a Dark Phototype: A Case Series

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Key words: dermoscopy, annularity, atrophic lichen planus, dark skin, case series

Citation: Kelati A, Rimani M, Chiheb S. Dermoscopy of Annular Atrophic Lichen Planus on a Dark Phototype: A Case Series. Dermatol Pract Concept. 2023;13(1):e2023024. DOI: https://doi.org/10.5826/dpc.1301a24

Accepted: May 26, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Annular atrophic lichen planus (AALP) is considered one of the rarest morphological variants of LP [1], it affects usually the limbs, penis, scrotum or intertriginous areas [2]. Histologically, AALP is characterized by an extensive elastolysis caused by lymphatic cells [3].

Dermoscopic findings of AALP have not been well described. The aim of this report is to investigate dermoscopic features of this rare variant of LP in dark skinned patients.

Case Presentation

Five dark-skinned patients (phototype V) with AALP were included in this case series. Patients ranged in age from 7 to 35 years (median age was 22.2 years), there was a male predominance (3/5 patients), 3 of these patients were adults, and 2 of them were children from the same family (the mother and her 2 children). No specific history has been noted.

All patients presented itchy papules, and plaques of annular morphology with a hyper-pigmented-atrophic center and a violaceous raised border, individual lesions ranged in size from 0.5 to 2 cm, the eruptions were located on the upper limbs in 2 adult patients, and generalized on the trunk, the back and the limbs in three patients from the same family. None of the patients had oral mucosal, vulval, scalp, or nail lesions.

Upon dermoscopic analysis, we observed mixed features of grayish-white annular and reticular Wickham Striae (WS) at the periphery of the lesions, and clustered brown-grey dots on a light brown background in the center (black-hole pattern). In active lesions, dotted vessels around WS were noticed on a background of erythema. In late lesions, we observed heterogeneous granular pigmented dots on and around WS, white starburst scar-like areas were noticed in some spots (Figure 1).
Histopathology was performed in adult patients, classic histopathology of lichen planus was observed at the periphery of the lesion, with hair damage in some areas, while in the center, the epidermis was atrophic and flattened, with loss of rete ridges. Melanophages were noticed in the papillary dermis (Figure 2). Based on these findings, the diagnosis of AALP was reached. Adult patients were treated with topical steroids and oral doxycycline, oral erythromycin was prescribed for the two children. Four of them went into complete remission, while in one patient with eruptive

**Figure 1.** Pigmented annular atrophic lichen planus (AALP). (A,B) Clinical pictures of eruptive AALP. (C) Localized AALP on the limbs and the axilla. (D-F) Dermoscopy images showing grayish-white annular and reticular Wickham striae (WS) at the periphery of the lesions, and clustered brown-gray dots on a light brown background in the center (black-hole pattern). (G) Active lesions: dotted vessels around annular WS on a background of erythema. (H,I) Late inactive lesions: heterogeneous granular and arciform pigmented dots and globules on and around WS (I), white starburst scar-like areas (H).
AALP, two recurrences occurred, and oral steroids were then prescribed with a good evolution.

Conclusions

The role of dermoscopy in diagnosing AALP in dark skin was highlighted in one case report [2] and one study [4], the black hole pattern that was reported in this study was mixed with other patterns of LP, also the authors reported an absence of vascular features. While, in our case series, the black hole pattern was the predominant pattern and vascular structures were noticed around WS on a background of erythema in active early lesions. In addition, we described dermoscopic findings of inactive late lesions of AALP such as heterogeneous granular pigmented dots and white starburst scar-like areas.

One the other hand, in the previous case report [2], another different dermoscopic pigmented pattern was reported, which is diffuse fine peppering or perifollicular pigmentation, this may be due to the different clinical
presentation in that case as annular macules without a raised edge, which explains the absence of the black hole pattern; that translates the difference of structures in the edge and the center of the annular atrophic lesion as it was described on histopathology.

This case series did not only highlight dermoscopic findings, but we also report some facts about this rare variant of LP. For instance, the familiar onset of the lesions is spurring the reflection of a specific genetic predisposition, especially in the eruptive subtype of AALP. Concerning the localized subtype of AALP, it was previously reported and described on male genitalia, intertriginous areas and extremities, and could be admixed with classic lesions of LP [5].

Acknowledgements

We are indebted to Constance Renton and Saadi Wafae for their help in the English editing of this manuscript.

References


Introduction

Colored sweat is a sporadic disorder, which can be due to apocrine, true eccrine and pseudo-eccrine chromhidrosis [1]. Pseudo-chromhidrosis is characterized by excretion of normal colorless sweat, which becomes colored following contact with products of chromogenic microbial or extrinsic chemicals on the skin surface [2]. There are very few case reports of pseudo-chromhidrosis [1-4]. Hereby, we present three sporadic case of red, black and pink pseudo-chromhidrosis.

Case Presentation

Case 1. An apparently healthy 10-year-old female presented with reddish discoloration of both palms for last 7 days. Her brother was also suffering from the similar complaint. Clinical examination revealed palmar creases with reddish secretion (Figure 1). Skin biopsy was negative for lipofuscin granules around eccrine orifices which ruled out apocrine chromhidrosis. Clinical diagnosis of pseudo-chromhidrosis was made.

Case 2. A 7-year-old boy presented with progressive darkening of both the palms since last 5 days. Skin biopsy was performed which supported the diagnosis of pseudo-chromhidrosis.

Case 3. A 36-year-old female, known case of rheumatoid arthritis presented with 10 days history of pink discoloration of both palms which aggravated with exertion. She did not give consent for biopsy. Clinical diagnosis of pseudo-chromhidrosis was made.

In all the three cases, color fade on rubbing with absolute alcohol. All patients denied intake of food, vitamin supplements, use of cosmetics or dyes that could have caused such discoloration. There was no specific odor or bleeding from any site. Psychological assessment was normal and family history was insignificant for all patients. Routine biochemical tests, gram staining, fungal scrapping and staining revealed no abnormality. All patients were prescribed oral erythromycin and topical clindamycin which resulted in complete relief with no recurrence for all patients.
Conclusions

Chromhidrosis, ie colored sweat can be produced by eccrine and apocrine glands. Eccrine chromhidrosis due to intrinsic factors is known as true eccrine chromhidrosis and secondary to extrinsic factors is known as pseudo-chromhidrosis. In pseudo-chromhidrosis, sweat produced is colorless but it becomes colored because of chromogen, which include chromogenic bacteria, chemicals, paints, dyes and self-tanning products [2].

Apocrine chromhidrosis is due to presence of increased amount of lipofuscin granules in apocrine glands and their excretion in sweat produces colored sweat [5]. While the diagnosis of eccrine chromhidrosis depends on detailed patient history and exclusion of ingestion of pigments, diagnosis of pseudo-chromhidrosis is based on exclusion of chromhidrosis and successful treatment with antibiotics or antiseptic scrub in this case. Thus, it is very important to distinguish between apocrine or eccrine chromhidrosis and pseudo-chromhidrosis as there is difference in management with different types. Pseudo-chromhidrosis can be treated with topical or systemic antibiotics and cessation of offending agents.

Although, pseudo-chromhidrosis does not constitute a health issue, it may cause psychological stress and social embarrassment. Thus, dermatologist must be aware of the various colors of chromhidrosis in order to determine its actual cause as pseudo-chromhidrosis is easily treatable with antiseptic scrub, topical, systemic antibiotics [2]. On detail literature scan, red pseudo-chromhidrosis has never been reported on palms and pink pseudo-chromhidrosis has been once been reported in the literature.

References


Combined Use of Dermoscopy, Reflectance Confocal Microscopy and Ex-Vivo Gene Expression Profiling to Detect a Micro-Melanoma Less Than 1 mm in Diameter

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Key words: reflectance confocal microscopy, dermoscopy, gene expression profiling, micro-melanoma, melanoma, skin cancer, early detection

Citation: Witkowski AM, Ludzik J, Chung J, Lee C, Leachman S, Pellacani G. Combined use of dermoscopy, reflectance confocal microscopy and ex-vivo gene expression profiling to detect a micro-melanoma less than 1 mm in diameter. Dermatol Pract Concept. 2023;13(1):e2023055. DOI: https://doi.org/10.5826/dpc.1301a55

Accepted: June 3, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Micro-melanomas, or melanomas < 2 mm in diameter, are increasingly reported making screening methods like the ABCD(E) acronym outdated. Early detection of melanoma remains the utmost important prognostic factor, therefore understanding how to utilize different diagnostic tools is necessary to optimize detection of melanoma at its earliest, most treatable stage. Using a combination of imaging and molecular techniques, we detected and confirmed a micro-melanoma in situ measuring 0.65 mm in diameter.

Case Presentation

A 61-year-old female with no prior history of skin cancer presented for a skin examination. Clinical examination of her right cheek revealed a tiny, hyperpigmented dot not previously noticed by the patient. Dermoscopy showed sun-damaged skin with a dark brown macule and asymmetric perifollicular hyperpigmentation. Reflectance confocal microscopy (RCM) revealed dendritic cells concentrated around a single hair follicle, consistent with folliculotropism (Figure 1). The final diameter incorporated the
farthest-reaching dendritic cell projections measuring at 0.65 mm. Initial histopathology showed a solar lentigo without atypia. Due to discordance with clinical-dermoscopic concern, deeper sections were requested and stained with Melan-A and SOX10 revealing irregular and heterogenous melanocytic nests and single melanocytosis, consistent with melanoma in situ (MIS) (Figure 2). Additionally, the sample underwent a diagnostic 23-gene expression profile (GEP)
test which returned a positive result (suggestive of malignancy). National Comprehensive Cancer Network (NCCN) guidelines make note of multiple ancillary diagnostic tests, which includes diagnostic GEP, that can help to differentiate equivocal melanocytic lesions and may be useful in cases of clinical discordance [1]. In the context of these ancillary findings final diagnosis of MIS was achieved. For control, four 5x5 mm RCM image sets of the epidermis, dermal-epidermal junction and upper dermis and two 2-mm punch biopsies were completed adjacent to the biopsy site in the most pigmented areas and no atypical features were found confirming the absence of residual tumor in nearby locations.

Conclusions

With the widespread adoption of dermoscopy, increasing numbers of micro-melanomas have been identified. Relying on dermoscopy alone, the smallest melanoma recorded measured at 1.3 mm [2] and another case enhanced by total-body imaging system reported a 0.9 mm diameter melanoma [3]. RCM is also a valuable second-level examination tool that combined with digital follow-up facilitates recognition of early-stage disease. Some argue that such small lesions cannot be malignant and investing in its detection is wasteful, however Regio Pereira et al evaluated 86 melanomas <5 mm in diameter which found 44% were invasive melanomas [4] highlighting the importance of investigating suspicious lesions regardless of size. Although our case demonstrated suspicious dermoscopy and RCM findings, initial histopathology reports were benign. Recognizing histopathology has limitations due to sampling bias, potentially missing up to 10% of melanomas [5], we requested additional staining and 23-GEP testing that ultimately revealed a diagnosis of MIS with a diameter of 0.65 mm. This case attests to the heightened diagnostic capabilities of multiple imaging and molecular tools when used in conjunction to confirm an early melanoma, which may result in better cosmetic, financial and patient morbidity.

References

Validation of the Turkish Version of the Skin Cancer Quality of Life Impact Tool (SCQOLIT): A Health-Related Quality of Life Questionnaire for Non-metastatic Melanoma and Non-melanoma Skin Cancer

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Key words: skin cancer, skin cancer related quality of life, melanoma, non-melanoma skin cancer

Citation: Karakok H, Bostanci S, Akay BN, Calıskan D, Ateş C, Köse K. Validation of the Turkish Version of the Skin Cancer Quality of Life Impact Tool (SCQOLIT): A Health Related Quality Of Life Questionnaire for Non-Metastatic Melanoma and Non-Melanoma Skin Cancer. Dermatol Pract Concept. 2023;13(1):e2023001. DOI: https://doi.org/10.5826/dpc.1301a1

Accepted: April 24, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Quality of life instruments (QoL) have been developed to measure the efficacy of treatments in chronic illnesses and cancers [1]. Skin cancers, including melanoma and non-melanoma (NMSC), are the third most common type of cancer worldwide and have been increasing in incidence [2].

There have been plenty of investigations on the QoL of patients with skin cancers and several instruments were developed [3-8]. There is only one instrument which was validated for non-metastatic skin cancers, the Skin Cancer Quality of Life Impact Tool (SCQOLIT) [9].

Numerous tools have been developed to measure QoL. Important characteristics of the tools are validity, reliability, interpretability, structure (using factor analysis or item response theory), responsiveness, interpretability, brief response burden and an acceptable administrative burden [10].

While both generic and specific tools are used to measure QoL in various types of chronic diseases, specific tools give more accurate information and may detect aspects not identified with generic tools [11].
There are two validated disease-specific QoL instruments for melanoma. The EORTC-MM was developed for metastatic melanoma. FACT-MM can assess all the stages of melanoma. Patients diagnosed with melanoma had lower emotional well-being on FACT-MM scale than normal population [12].

There are several instruments developed for the assessment of QoL of patients with NMSC. The questionnaire developed by Esser et al, was made to assess the health status of patients with basal cell carcinoma (BCC) before a surgical procedure. It is not clear whether this tool may be used to evaluate QoL and the reliability of the tool has not been investigated [13]. SCQoL was developed from a questionnaire originally developed to evaluate the QoL in patients with actinic keratosis. Only the term ‘sun damage’ has been changed as ‘skin cancer’ for this tool. It is not clear if this tool is able to measure all the aspects affected by skin cancer [14].

Facial Skin Cancer Index was developed for NMSC located on the head and neck region. The validity and reliability are well established, the instrument is designed to measure the dimensions affected by NMSC. On the other hand, it cannot be used for NMSC located anywhere but the head and neck region [5].

A specific QoL tool BasQol was developed by Waalboer-Spuij et al. face, content and construct validation, reliability and internal consistency of BasQol was proven. The validation of the English version of BasQol is currently being searched. The tool is designed for BCC and squamous-cell carcinoma (SCC) [15].

The only validated tool which is used in non-metastatic skin cancer types is the SCQOLIT. The SCQOLIT was shown to have construct and external validation, reliability, internal consistency and responsiveness [9]. Wali et al also showed feasibility of this tool in dermatology skin cancer clinics for patients with NMSC [16].

### Objectives

The objective of this study is to validate the Turkish version of the Skin Cancer Quality of Life Impact Tool (SCQOLIT) [9]).

The translation and validation of the Turkish version of the SCQOLIT provides a tool that can be used to measure QoL of NMSC in Turkish populations. The current study aims to investigate internal validation, construct validation, external validation and convergent validity, reliability and internal consistency of the Turkish version of the tool.

### Methods

The study was carried out at Ankara University School of Medicine, Department of Dermatology and Venereology between December 2015 and September 2016.

The SCQOLIT was originally developed by Burdon-Jones et al to measure the QoL of patients with non-metastatic skin cancers. The permission for the translation and validation of the tool was granted by Burdon-Jones. The tool was translated into Turkish by 2 specialists in the Department of Dermatology and by a scientist of Foreign Languages Department in accordance with international translation guidelines. Three documents were created. One by the 2 specialists of Dermatology. The other two by independent translators who translated it back to English. The text was evaluated by a scientific team including a foreign linguist and a specialists of Dermatology.

A total of 141 patients who had been diagnosed and treated for skin cancer within the previous 3 months were included in this study. Patients younger than 18 years and patients with impaired cognitive functions and illiterate patients were excluded from the study.

Confirmatory factor analysis was used for the internal validation of the SCQOLIT. Comparative compliance statistics (Comparative Fit Index [CFI], Tucker-Lewis Index [TLI], Root Mean Square Error of Approximation [RMSoA]) were used to evaluate the efficacy of the model which was produced as a result of the confirmatory factor analysis.

The Dermatology Quality of Life Index (DLQI) was translated into Turkish and has been used in various studies since. The DLQI was used for external validation of the SCQOLIT. The hypothesis to be tested was whether DLQI and SCQOLIT had same directional correlations.

The SCQOLIT was tested to discriminate melanoma and NMSC to evaluate the convergent validity.

The internal consistency was assessed by using Cronbach alpha and intraclass correlation coefficient (ICC) in terms of reliability (defined by test-retest method).

Demographic characteristics of the patients and tumor characteristics were recorded to investigate their impact on QoL. Mplus trial version and SPSS 20.0 programs were used for statistical analyses.

For BCC, size and location of the tumor, primary or recurrent origin, histopathological subtype, presence or lack of perineural invasion, history of radiotherapy at the site of the tumor and immunological status of the patient were recorded to assess risk analysis. For SCC, size and location of the tumor, primary or recurrent origin, histopathological features (differentiation, tumor thickness, presence of perineural, lymphatic or vessel invasion), immunological status of the patient, history of radiotherapy and the presence of a chronic inflammation or a scar at the site of the tumor were recorded to assess the risk analysis. High risk tumor features were classified in accordance with NCCN guidelines [17]. Melanoma risk analysis was conducted in accordance with the NCCN guidelines [18]. Breslow thickness, Clark level, ulceration, presence of regression, and mitosis rate were recorded to define the stage of the melanoma.
The Ethics Committee Approval was granted (10-439-16) All the participants gave written informed consent.

Results

The mean ages were 63.75 ± 12.07, 66.53 ± 13.55, 49.24 ± 16.67 in patients with BCC (N = 65), SCC (N = 30) and melanoma (N = 46), respectively. Twenty-nine of the patients with BCC, 11 of the patients with SCC and 24 of the patients with melanoma were females (Table 1).

Patients data, number of nevi, personal and family history of skin cancer, Fitzpatrick skin type and treatment modality are shown in Table 2.

Thirty-eight BCC (N = 65) and 10 SCC (N = 30) had high risk features. Forty melanoma patients were found to be at the first stage and 6 of them were at the second stage (Table 1).

| Table 1. Age, gender, risk classification of non-melanoma skin cancer and stage of melanoma |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Mean age | Gender | Risk classification of non-melanoma skin cancer: |
| | | Female | Male | High risk | Low risk |
| BCC (n=65) | 63.75 ±12.07 | 29 | 36 | 38 | 27 |
| SCC (n=30) | 66.53±13.55 | 11 | 19 | 10 | 20 |
| Melanoma stage: |
| Stage 1 | Stage 2 |
| M (n=46) | 49.24 ±16.67 | 24 | 22 | 40 | 6 |

| Table 2. Sociodemographic features of the patients |
|---------------------------------|---------------------------------|---------------------------------|
| Number of patients | Median score of the SCOQLIT (min-max) | Mean score of the SCOQLIT ± SD |
| Age |
| ≤65 | 83 | 11 (0-28) | 12.25 ± 7.038 |
| > 65 | 53 | 6 (0-28) | 7.81 ± 6.864 |
| Gender |
| Female | 64 | 11 (0-28) | 11.59 ± 7.648 SS |
| Male | 77 | 9 (0-28) | 9.65 ± 7.045 |
| Number of nevi |
| <100 | 125 | 9 (0-28) | 10.41 ± 7.42 |
| >100 | 16 | 10 (3-28) | 11.50 ± 7.04 |
| History of skin cancer |
| Positive | 108 | 12 (0-27) | 12.36 ± 7.61 |
| Negative | 33 | 9 (0-28) | 9.97 ± 7.22 |
| Family history of skin cancer |
| Positive | 23 | 12.5 (0-27) | 11.81 ± 8.07 |
| Negative | 119 | 9 (0-28) | 10.52 ± 7.59 |
| Fitzpatrick skin type |
| Type 1 | 1 | 17 | 17 |
| Type 2 | 53 | 9 (0-28) | 10.51 ± 7.1 |
| Type 3 | 74 | 9 (0-28) | 10.04 ± 7.49 |
| Type 4 | 13 | 10 (5-28) | 12.92 ± 7.79 |
| Treatment modality |
| Imiquimod | 1 | 1 | 1 |
| Cryotherapy | 1 | 28 | 28 |
| Imiquimod + excision | 1 | 7 | 7 |
| Primary excision | 89 | 9 (0-27) | 10.44 ± 7.49 |

Table 2 continues
The relationship between age and QoL was found to have a statistically significant negative correlation ($r = -0.333$, $P < 0.001$). Patients under the age of 65 had poorer QoL (Table 4).

There was no statistically significant relation with gender and QoL ($P = 0.101$). Personal and family history of skin cancer had no effect on QoL ($P = 0.099$, $P = 0.132$ respectively).

There was neither statistically significant relation between Fitzpatrick skin type, the number of Nevus and QoL ($P = 0.589$, $P = 0.536$).

Furthermore, high-risk tumor characteristics in non-melanoma skin cancer and stage of melanoma had no impact on QoL ($P = 0.235$ for BCC, $P = 1.00$ for SCC, $P = 0.635$ for melanoma).

**Conclusions**

In the current study, the Turkish version of the tool was shown to have internal validation, construct validation, external validation and convergent validity, reliability and internal consistency. The factor load of question 3 was lower than 0.4 indicating the inadequacy of this term in predicting QoL, a point that the original study did not mention. Internal validity of the Turkish version of the SCQOLIT was excellent (Cronbach alpha = 0.863). Test-re-test correlation coefficient was found as high as 0.824 (%95 confidence interval $0.644 - 0.918$).

The scores for SCQOLIT and DQLI were both statistically significant with same directional correlations, confirming external validity of the tool.

To test the convergent validity of the SCQOLIT, the total score of the patients with melanoma and non-melanoma skin cancer was compared. Total score of the SCQOLIT in patients with melanoma was statistically significantly higher than NMSCs indicating the tool ability to discriminate these 2 skin cancer types ($P = 0.024$) (Table 3).

The administrative and response burden of the tool was found to be quite low as it took 2.5 to 4 minutes to respond to all the questions and the recording process of the data was easy.

The SCQOLIT was shown to have one dimensional structure in the original study. In the current study, the question items of the Turkish version of the SCQOLIT were assessed with confirmatory factor analysis to demonstrate tools one-dimensional structure. The compliance to the model was found to be efficient (CFI:0.952, TLI:0.938, RMSEA0.102). Most of the question items had a factor load greater than 0.4 except for question 3 with a factor load of 0.372, indicating the inadequacy of this question in predicting QoL, a point that the original study did not mention. Internal validity of the Turkish version of the SCQOLIT was excellent (Cronbach alpha = 0.863). Test-re-test correlation coefficient was found as high as 0.824 (%95 confidence interval $0.644 - 0.918$).

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### Tables

<table>
<thead>
<tr>
<th>Table 2. Sociodemographic features of the patients. (continued)</th>
</tr>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Excision+ sentinel lymph node dissection</td>
</tr>
<tr>
<td>Excision+ flap or graft procedure</td>
</tr>
<tr>
<td>Amputation</td>
</tr>
<tr>
<td>Radiotherapy</td>
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<tr>
<td>Vismodegib</td>
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</table>

<table>
<thead>
<tr>
<th>Table 3. Mean and median total score of the SCQOLIT in patients with melanoma and NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median score of the SCQOLIT (min-max)</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
<tr>
<td>NMSC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Total Score of the SCQOLIT of patients under and above the age of 65</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>≤65</td>
</tr>
<tr>
<td>≥65</td>
</tr>
</tbody>
</table>
The mean scores of SCQOLIT of the patients with melanoma were similar in both the current and the original study. On the other hand, the mean scores (mean = 9, range 0-28) of the SCQOLIT of patients with NMSC in the current study was higher than those in the original study (mean = 4, range 0-19).

The percentage of patients with SCC in the present study was 31.6% whereas it was 10% in the original study. Additionally, 58.4% of all BCCs had high risk features in the current study. The original study did not mention the risk classification and the percentage of the high-risk tumors in their population [9]. These findings might be related with the differences between populations.

In terms of factors that might impact SCQOLIT scores in current study was age. Age was shown to be the only factor having a statistically significant impact on SCQOLIT. There was a negative correlation between age and the scores. Patients under the age of 65 had poorer QoL. The lower median age of the study population in the current study compared with the original study might be the explanation of this result. El Abbadi et al also found a negative correlation between skin cancer and patients age, gender and location of the tumor [19]. While similar results were also observed in the literature, some investigators found no relation between age and QOL [20-25].

There was no statistically significant relation between previous skin cancer history and QoL in the present study. Rhee et al found that in patients with NMSC the history of previous skin cancer had a negative impact on QOL in contrast to Steinbauer et al who observed no relation [24,25].

Current study has a very limited number of patients with melanoma, and findings showed no relation between QoL and a positive family history of melanoma. Barbato et al found that patients with melanoma who had a positive family history of melanoma had better QoL scores [26].

Both the current study and the original study found no relationship between Melanoma Breslow Thickness and QoL while Holterhouse et al observed that the stage of the tumor (stage 0-2) had a negative impact on QOL [9,27]. We found no relation between Fitzpatrick skin type or high-risk tumor features and QoL in the current study.

As the current study aimed to validate the Turkish version of the SCQOLIT, the sample size was too small (not large enough) to investigate and demonstrate the relation between QoL and age, Fitzpatrick skin type, personal or family history of skin cancer, stage or high-risk tumor features. This was the main limitation of the study. Further studies with larger patient groups and repeated SCQOLIT in defined timeframes could be planned to investigate the relation between age and QoL.

In conclusion, the translation and validation of the Turkish version of the SCQOLIT provides a valid tool that can be used to measure QoL of non-metastatic skin cancers in Turkish- speaking populations. This tool can be used to investigate QoL and many parameters mentioned above in further studies.

References


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Preliminary Dermoscopic Features of Discoid Lupus Cheilitis in Eight Patients of Skin of Color

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Key words: cheilitis, dermoscopy, lupus, pigmentation

Citation: Behera B, Kumari R, Srinivas BH, Ch Toi P, Gochhait D, Ayyanar P. Preliminary Dermoscopic Features Of Discoid Lupus Cheilitis In Eight Patients Of Skin Of Color. Dermatol Pract Concept. 2023;13(1):e2023045. DOI: https://doi.org/10.5826/dpc.1301a45

Accepted: September 14, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Discoid lupus cheilitis (DLC) is a spectrum of discoid lupus erythematosus (DLE) presentation that can occur in association with cutaneous lesions. Dermoscopic features of DLC are sparsely reported [1,2].

Case Presentation

All eight patients in our series were female. They belonged to Fitzpatrick skin phototypes IV and V. The clinical and dermoscopic details of all the patients are mentioned in Table 1. One case tested positive for antinuclear antibody by immunofluorescence method (2+). The pathological features in all the cases were consistent with DLC. Direct immunofluorescence (single case from the lip and four patients from skin lesion) showed linear deposition of IgG, IgM, IgA, and or C3 along the basement membrane zone.

Cheilitis results from a vast group of disorders ranging from simple lip licking to malignant neoplasms, such as squamous cell carcinoma (SCC). Morphologically DLC can be small papules, discoid plaques, or can diffusely involve either of the lips. Different morphological variations like dyspigmentation, erosion, keratotic, atrophic, and rare hypertrophic subtypes have been described. Early diagnosis is essential as it can cause significant lip disfigurement and can rarely progress to SCC [3]. The diagnosis can be challenging in the absence of other mucocutaneous lesions of DLE.

The dermoscopic features, homogenous purplish-white, ivory-white to reddish-white areas, brown to blue-gray dots, globules, and peppering, and polymorphous vascular pattern, observed by us are the direct reflection of the underlying pathology of discoid lupus (Figures 1 and 2). The white color corresponds to the hyperkeratosis with or without acanthosis, the red color to the increased vascularity, the brown to brown-gray dots and globules to melanin in the
stratum corneum and/or epidermis, blue-gray dots and globules to the dermal melanin incontinence and melanophages, and the vascular structures to the dilated dermal vessels. Other features noted were erosion, scales, and crust. The brown to blue-gray dots, globules, and peppering were distributed diffusely or in clusters. The polymorphous vascular pattern included linear, linear curved, and linear vessels with branches. The observed vessels tortuosity and the absence

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Demographic, clinical and dermoscopic features (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td>1. Age: 29-56 years</td>
</tr>
<tr>
<td></td>
<td>2. Gender: Female (8)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td>1. Location of cheilitis</td>
</tr>
<tr>
<td></td>
<td>i. Lower lip (7)</td>
</tr>
<tr>
<td></td>
<td>ii. Both the lips (1)</td>
</tr>
<tr>
<td></td>
<td>2. Morphology of cheilitis</td>
</tr>
<tr>
<td></td>
<td>i. Eroded plaque surrounded by brown, gray, or violaceous pigmentation with/without crusting (4)</td>
</tr>
<tr>
<td></td>
<td>ii. Erythematous to violaceous scaly plaques surrounded by violaceous to brown pigmentation (2)</td>
</tr>
<tr>
<td></td>
<td>iii. Atrophic plaque surrounded by gray-brown pigmentation (2)</td>
</tr>
<tr>
<td>3. Associations</td>
<td>i. Cutaneous DLE (3) Verrucous DLE (1)</td>
</tr>
<tr>
<td></td>
<td>ii. Eyelid DLE (1)</td>
</tr>
<tr>
<td>Dermoscopic characteristics</td>
<td>1. Scales (7)</td>
</tr>
<tr>
<td></td>
<td>i. Color</td>
</tr>
<tr>
<td></td>
<td>• White (7)</td>
</tr>
<tr>
<td></td>
<td>• Yellow (1)</td>
</tr>
<tr>
<td></td>
<td>ii. Distribution (could not be evaluated due to the use of immersion fluid)</td>
</tr>
<tr>
<td></td>
<td>3. Vessels (8)</td>
</tr>
<tr>
<td></td>
<td>i. Morphology</td>
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<tr>
<td></td>
<td>• Linear (8)</td>
</tr>
<tr>
<td></td>
<td>• Linear curved (hairpin) (7)</td>
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<tr>
<td></td>
<td>• Linear vessels with branches (2)</td>
</tr>
<tr>
<td></td>
<td>• Dotted (0)</td>
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<td></td>
<td>ii. Distribution</td>
</tr>
<tr>
<td></td>
<td>• Uniform (2)</td>
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<td></td>
<td>• Clustered (2)</td>
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<td></td>
<td>• Peripheral (4)</td>
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<td></td>
<td>• Reticular (0)</td>
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<tr>
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<td>• Unspecific (1)</td>
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<td>3. Follicular or eccrine findings:</td>
<td>Follicular plugging at the mucocutaneous junction (1)</td>
</tr>
<tr>
<td></td>
<td>a. Other structures: Homogenous area</td>
</tr>
<tr>
<td></td>
<td>i. Ivory-white homogenous area (6)</td>
</tr>
<tr>
<td></td>
<td>ii. Reddish-white homogenous area (5)</td>
</tr>
<tr>
<td></td>
<td>iii. Purplish-white homogenous area (4)</td>
</tr>
<tr>
<td></td>
<td>iv. Peripheral irregular brown-gray to blue-gray structureless area (7)</td>
</tr>
<tr>
<td></td>
<td>b. Dots, globules, fine and coarse peppering (8)</td>
</tr>
<tr>
<td></td>
<td>i. Color: Brown, brown-gray to blue-gray</td>
</tr>
<tr>
<td></td>
<td>ii. Arrangement</td>
</tr>
<tr>
<td></td>
<td>• Clustered (6)</td>
</tr>
<tr>
<td></td>
<td>• Diffuse (3)</td>
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<tr>
<td></td>
<td>c. Lines</td>
</tr>
<tr>
<td></td>
<td>i. Brown to blue-gray radial lines (7)</td>
</tr>
<tr>
<td></td>
<td>ii. Peripheral purplish-white radial striations (6)</td>
</tr>
<tr>
<td></td>
<td>d. Erosion (4)</td>
</tr>
<tr>
<td></td>
<td>e. Crust (5)</td>
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<td></td>
<td>f. Blood spot (2)</td>
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</table>

DLE = discoid lupus erythematosus.
of dotted vessels were other notable features. There was no difference in dermoscopic features relating to the duration of the lesions.

Also, we observed two new dermoscopic features in DLC, brown to blue-gray radial lines and peripheral purplish-white radial striations. A case of actinic cheilitis reported having peripheral, white-colored projections. The role of dermoscopy in diagnosing DLC needs to be evaluated in larger studies [4]. In one case, we observed follicular plugging at the mucocutaneous junction. This particular feature may favor DLC diagnosis as it is commonly observed in cutaneous DLE.

Dermoscopic features described for labial DLE are white structureless areas, scales, erosion, brown pigment spots, telangiectasia, and bleeding spots [1]. An isolated case from India had a pink background, whitish to yellowish scales, white structureless areas, blood spots, telangiectasia, irregular vessels, and peripheral grayish-black dots [2]. The dermoscopic
Conclusions

In conclusion, we describe the preliminary dermoscopic features of DLC in eight patients with skin of color. The common dermoscopic features were homogenous purplish-white, ivory-white to reddish-white areas, brown to blue-gray dots, globules, and peering along with a polymorphous vascular pattern.

features described for lip lichen planus, a closest differential of DLC, are Wickham striae, ulcer, brown to blue-gray dots, globules, and peering, scales, linear, hairpin and dotted vessels [5].
References


Facial Bier Spots Unresponsive to Botulinum Toxin: A Case Series

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¹Department of Dermatology and Venereology, University of Health Sciences, Gulhane Training and Research Hospital, Ankara, Turkey

Introduction

Bier spots are asymptomatic, irregular anemic macules in a blanchable erythematous background. However, the pathogenesis is not clear yet; abnormal vasoconstriction of vessels has been suggested as the primary mechanism [1]. Lesions often involve extremities and the trunk; only one case with facial involvement has been reported previously [2]. Lesions do not require specific treatment, but patients may experience cosmetic problems [3].

Herein, we described 3 cases with Bier spots on the face with accompanying tension-type headaches in all patients and tested the hypothesis that botulinum toxin might improve facial Bier spots.

Case Presentation

A 45-year-old male patient (Patient 1) was admitted to our outpatient dermatology clinic with a complaint of pale, whitish macules on the forehead. The complaints had started six months ago after trauma and become more visible with emotional stress and bending down. He also suffered from headaches and forehead wrinkles. A diagnosis of Bier spots was made upon clinical examination. Laboratory evaluations and imaging methods revealed no abnormalities. A total of 150 Speywood units (reconstituted with 2.5 ml normal saline) of botulinum toxin (AbobotulinumtoxinA, Dysport®, Ipsen, 500 units) were injected to forehead lines considering the localization of Bier spots (Figure 1). In addition to cosmetic improvement of the frontal wrinkles within one week, headache severity regressed from 10 to 5 points according to the visual analog scale (VAS) for pain. Unfortunately, there was no response in Bier spots six weeks after botulinum toxin injection.

The symptoms of a 48-year-old male patient (Patient 2) started one year ago on the trunk and face without any triggering (Figure 2). A 32-year-old female patient (Patient 3) had experienced similar complaints on the forehead six months after her first vaginal delivery. Strikingly, both were accompanied by tension-type headaches. Laboratory evaluations and imaging methods of both patients did not reveal any abnormality.
Figure 1. Case 1. (A) Pretreatment. Bier spots were marked with black color to orient the injector. The hypopigmented macule highlighted with a red arrow was selected as a control area, and no injection was performed. (B) Post-treatment. Significant improvement was recorded in forehead lines at week 1, while there was no improvement in Bier spots.

Figure 2. Case 2. The patient provoked these lesions by holding his breath for about a half minute and bending down just before the photographs.
Botulinum toxin injections were performed to Bier spots on the forehead of the patient 2, similar to Patient 1. While no improvement was observed in Bier spots at the end of the 6th week, the headache severity regressed from 10 to 2 points after one week according to the VAS score. Patient three recommended no treatment due to breastfeeding.

Conclusions

Recently, botulinum toxin in non-cosmetic medical conditions, including tension-type headaches, is becoming increasingly popular. Considering its effects on the cutaneous vasculature [4-6], we aimed to test the hypothesis that botulinum toxin might relax the muscles around the small arterioles and increase transcutaneous blood flow, thereby reducing hypoxia and improving Bier spots. Possible common pathogenesis for the coexistence of both diseases appears to be genetic and triggering factors for an exaggerated vasoconstrictive response [1,6]. However, while tension-type headaches in both patients improved, Bier spots did not. Therefore, failure to botulinum toxin may be related to insufficient dosage or other unknown factors that play a role more critical than the exaggerated vasoconstrictive response.

References

Introduction

Cumulative solar exposure has been studied for years. In 1951, nodular cutaneous elastosis with cysts and comedones on sun damaged skin was described as Favre-Racouchot syndrome [1]. It usually manifests as symmetrical lesions on the periorbital or temporal areas and mostly affects older men [2]. The ectopic form of this syndrome, called actinic comedonal plaque, has rarely been reported and presents with lesions mainly on the upper extremities. However, there is a lack of dermoscopic descriptions of this entity.

Case Presentation

A 59-year-old female smoker, phototype IV, presented with two plaques on her arms that had been growing for the last two years. The first lesion, on the lateral aspect of the left arm, was an erythematous cribiform plaque, surrounding a central atrophic area, with comedones and small cysts (Figure 1A). The second lesion, on the right forearm, consisted in an area of few grouped erythematous papules, with comedones (Figure 1B). Dermoscopy (DermLite Cam®, magnification 10×, polarized capture with immersion fluid) showed an erythematous background, scar-like depigmentation areas, chrysalides and fine linear irregular vessels. In the central area, small islands of normal skin could be visualized, while at the periphery of the plaques there were milia cysts and comedones on (Figure 2, A and B). Possible dermoscopic differential diagnosis included colloid milium, milia, syringoma, discoid lupus and trichoepithelioma. Histopathology revealed accentuated infundibular dilatation with follicular plugging (seen clinically and dermoscopically as milia cysts and comedones) and circumjacent fibrosis with loss of elastic fibers (Figure 3), which corresponded to areas of the scar-like depigmentation and chrysalides on dermoscopy. Based on the clinical and histopathologic
findings, the diagnosis of actinic comedonal plaque was established.

The actinic comedonal plaque is a variant of Favre-Racouchot syndrome, which can be found on sun damaged skin, such as the forearms. It was first described by Eastern et al in 1980 in five fair-skinned men older than 50 years of age [3]. The pathogenesis is uncertain, but excessive chronic UV exposure, cigarette smoking and radiation therapy seem to be risk factors [4]. The disease can be associated with actinic keratosis, cutis rhomboidalis nuchae and even squamous cell carcinoma [5]. Histology reveals marked solar elastosis, epidermal and sebaceous gland atrophy, and enlarged dilated
pilosebaceous infundibulum with regularly stratified epithelium. Comedones are similar to those of acne vulgaris [4]. The differential diagnosis includes actinic granuloma, chloracne, acne vulgaris, milia cysts, sebaceous gland hyperplasia, syringoma and trichoepithelioma [1]. Treatment remains a challenge, with reports describing the use of CO2 laser, retinoic acid cream, retinoid acid peeling and cryotherapy [3,5]. We prescribed a daily use of topical adapalene gel 1mg/g for our patient, however she was lost to follow-up during the COVID-19 pandemic and we were unable to evaluate the clinical response.

Conclusions

To the best of our knowledge, this is the first description in the literature regarding the dermoscopic features of the actinic comedonal plaque. We observed a clinical cribriform border, along with a dermoscopic central area with an erythematous background, chrysalides and fine linear irregular vessels. In addition, milia cysts and comedones were also visualized. Therefore, dermoscopy may be an additional tool for the assessment of this condition, improving the ability to identify structures in order to establish the correct diagnosis.

References

An Unexpected Dermatophyte? Two Remarkable Cases of Tinea Barbae by Trichophyton benhamiae

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¹Dermatology Department, Hospital de Fuenlabrada. Fuenlabrada, Madrid, Spain

Key words: Trichophyton benhamiae, Arthroderma benhamiae, tinea barbae, dermatophytosis, terbinafine


DOI: https://doi.org/10.5826/dpc.1301a37

Accepted: June 13, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Trichophyton (T.) benhamiae is considered an emergent zoophilic dermatophyte, with more cases being reported from various countries around the world. We hereby present two cases of tinea barbae by T. benhamiae.

Case Presentation

Case 1. A 48-year-old man attended the emergency department with a 1-month history of facial lesions treated with cloclopirox and mupirocin ointment. He had a healthy pet dog. On examination, he had extensive impetiginized crusts all over the nasolabial triangle. Removal of the crusts revealed erythematous, vegetating plaques on the nasolabial folds (Figure 1).

Case 2. Another 50-year-old man, owner of a healthy dog, came to the outpatient clinic complaining of a two-week facial rash previously treated with topical clobetasol and gentamicin without improvement. On examination he had an erythematous plaque on his chin, with some pustules and erosions covered by serous-hematic crust, and a 2-3 cm nodule in the plaque’s border (Figure 2). Some of his closest family members were being treated for tinea corporis.

Scales were gathered for fungal culture. In both cases, T. benhamiae was identified by MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) mass spectrometry analysis. Terbinafine 250 mg daily for three months completely cleared the lesions in both patients.

Conclusions

T. benhamiae, previously known as Arthroderma (A.) benhamiae, is nowadays a species on its own according to the latest dermatophyte taxonomy, based on the analysis of the internal transcribed spacer (ITS) ribosomal DNA region [1,2].

Every year, more cases of T. benhamiae are being reported worldwide particularly among children. This zoophilic dermatophyte is mainly transmitted by guinea pigs,
and seldom by other infected animals like rabbits, cats, dogs and even a fox [3]. Our patients were both adults and only had contact with their pet dogs, which were apparently unaffected; however, we have no information about their veterinary evaluation. Retrospectively our patients couldn’t remember being near a guinea pig, which can be silent carriers of *T. benhamiae* [4]. We haven’t found studies about *T. benhamiae* colonization in dogs.

Clinically, it usually causes highly inflammatory tinea corporis and faciei which can be confused with impetigo, delaying a correct diagnosis [5]. There are scattered reports of kerion celsi and onychomycosis [3,5]. To the best of our knowledge, only one case of tinea barbae by *T. benhamiae* has been previously reported by Braun et al in 2013, a 24-year-old male in which the authors identified *A. benhamiae* by PCR in the patient and in his guinea pig [6].

Identification of *T. benhamiae* requires molecular methods due to its similarity to other fungal species in standard cultures. Yellow subtype of this fungus grows in colonies that may be diagnosed as *Microsporum canis*, and the unusual white subtype is usually identified as *T. mentagrophytes*. Polymerase chain reaction (PCR) of the ITS region and MALDI-TOF both allow for a correct diagnosis [7].

Treatment is akin to that of other dermatophyte infections. If the infection covers an extensive area or hair follicles are affected, oral treatment is preferred, terbinafine being the first choice [3,5].

Tinea barbae by *T. benhamiae* seems to be rare. Previous contact with animals, especially guinea pigs, and inflammatory lesions on physical examination should prompt the diagnosis of *T. benhamiae* infection. Molecular diagnostic methods like PCR and MALDI-TOF are necessary to ensure correct identification of this emergent dermatophyte.

**References**


Regression of Multiple Melanocytic Nevi in Two Patients on Nivolumab for Metastatic Melanoma

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Key words: nivolumab, regression, melanocytic nevi, melanoma, dermoscopy


Accepted: May 26, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Immunotherapy (anti-PD1 and anti-CTLA4) has been described to achieve complete regression of non-metastatic melanoma, assessed by reflectance confocal microscopy; however, their effects on benign melanocytic lesions have not been thoroughly studied and may be underreported [1]. Herein we report 2 patients with regression of multiple nevi while on treatment with nivolumab for metastatic melanoma.

Case Presentation

Two patients, suffering from metastatic melanoma treated with nivolumab (Table 1), attended our outpatient clinic for their annual digital dermoscopic monitoring. They were not aware of any changes or new melanocytic lesions. On physical examination, no new lesions were detected since their last visit one year before; with dermoscopy several of their benign melanocytic nevi had lightened and no atypical or malignant lesions were observed (Figures 1 and 2). Both patients had experienced disease progression despite anti-PD1 treatment.

Conclusions

Benign melanocytic nevi regression is an emerging secondary effect of anti-PD1 drugs nivolumab and pembrolizumab. Although these drugs are used on other cancer treatments, this secondary effect seems to be more frequent in patients undergoing treatment for melanoma [2]. In an observational study published in 2017, 11 patients treated
with anti-PD1 for metastatic melanoma (10 with pembrolizumab and 1 with nivolumab) had more lightened nevi than controls during follow-up (49% versus 19%); nevertheless, differences were not statistically significant [3]. Lightening without halo is a known phenomenon, especially in patients treated with pembrolizumab [4,5]. There are few reports regarding regression of melanocytic nevi in patients treated with nivolumab: one similar to our patient, with no inflammation or halo, and another patient who experimented inflammation before regression, with no halo [6,7]. Though some articles suggest that regression of melanocytic nevi may be related to the therapeutic effect of the anti-PD1 drug and could be interpreted as a sign of good therapeutical response, our patients both experimented progression despite nivolumab treatment; therefore, more studies are required to shed light on this matter [2,5,7]. One of our patients also had vitiligo-like phenomenon, which has been suggested to be associated with a better prognosis [2].

Furthermore, some other questions remain still unanswered: it could be asked why some patients experience only lightening without halo, while others have vitiligo-like reactions and halo nevi, and whether the underlying mechanism is the same [3]; why some patients have clinical inflammation but most of them do not according to the literature. Lastly, it is debatable whether regression of nevi with anti-PD1 is as rare as it seems today, for it may be an unnoticed secondary effect in other cancer patients (lung, Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Metastatic melanoma</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age, years</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Location</td>
<td>Abdomen</td>
<td>Back</td>
</tr>
<tr>
<td>Mutation</td>
<td>BRAF V600E/E2/D</td>
<td>No</td>
</tr>
<tr>
<td>Treatment before/after nivolumab</td>
<td>Before: dabrafenib-trametinib, which was stopped because metastases spread to his lungs and inguinal and retroperitoneal lymph nodes (lymphadenectomy was performed)</td>
<td>No</td>
</tr>
<tr>
<td>Nivolumab start and end dates/doses mg/weeks</td>
<td>2021 – ongoing/ 240 mg every 2 weeks</td>
<td>2020-2021/ 480 mg every 4 weeks</td>
</tr>
<tr>
<td>Lightening of nevi observed with digital dermoscopy</td>
<td>2021: &gt; 80% of his nevi. (Previous digital monitoring: 2020)</td>
<td>2022: &gt; 60% of his nevi. (Previous digital monitoring: 2021)</td>
</tr>
<tr>
<td>Nivolumab secondary effects</td>
<td>Yes, vitiligo-like lesions</td>
<td>Yes, nivolumab-induced thyrotoxicosis and subsequent hypothyroidism</td>
</tr>
<tr>
<td>Disease progression while on nivolumab</td>
<td>Yes, new lymph node metastases near his melanoma scar on the abdomen and small bowel metastases (2022)</td>
<td>Yes, dermal melanoma metastases on the back (2021)</td>
</tr>
<tr>
<td>Second melanoma while on treatment</td>
<td>Yes, melanoma in situ on his back while on dabrafenib-trametinib (2020).</td>
<td>Yes, melanoma on his right leg (Breslow thickness 3.4 mm) while on nivolumab (2021).</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>A lung adenocarcinoma was diagnosed while on nivolumab (2021) and later excised. He has developed mediastinal lymph node metastases, awaiting treatment.</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Clinical images of patient 1: 2020 (left) and 2021 (right). Three examples of lesions registered in digital monitoring of patient 1. (A1-C1) First row shows these benign melanocytic in 2020. (A2-C2) Second row shows the same lesions one year later in 2021, 6 months after starting treatment with nivolumab.

kidney, head, and neck, etc.) who are not followed up in a dermatology clinic.

One may well wonder about the utility of digital monitoring of patients with metastatic melanoma undergoing treatment with immune checkpoint inhibitors (ICI). In a recent single-center retrospective cohort study 42 patients (1.9%) with metastatic melanoma who received treatment with ICI developed new melanomas; thus, prospective studies with longer follow-up are needed to draw a solid conclusion [8]. While on ICI, both of our patients had a second melanoma that was detected in the digital follow-up; we want to highlight that in case 1, with longer digital monitoring, melanoma was detected in situ, in line with the findings of Lallas et al where almost 70% of second primary melanomas detected during surveillance were in situ [9]. We think that, when available and feasible, monitoring with digital dermoscopy and total body photography should be offered to all melanoma patients, as it helps in the early diagnosis of melanoma, with some lesions being only diagnosed by dermoscopic changes in the absence of melanoma-specific criteria [9].

Regression of multiple nevi is a scarcely reported secondary effect of nivolumab we should be aware of, especially in dermoscopic monitoring. It may be an overlooked effect because patients treated with anti-PD1 for cancers other than melanoma are not usually examined by a dermatologist. Its prognostic meaning is still unclear.
References


Figure 2. Clinical images of patient 2: 2021 (left) and 2022 (right). Three lesions registered in digital monitoring of patient 2. (D1-F1) First row shows these benign melanocytic nevi in 2021, while on nivolumab treatment. (D2-F2) Second row displays the same lesions one year later in 2022, 6 months after finishing treatment with nivolumab.

A Case of Metastatic Basosquamous Basal Cell Carcinoma Treated With Carboplatin and Paclitaxel

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Key words: basal cell carcinoma, vismodegib, chemotherapy, carboplatin, metastatic


Accepted: April 28, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Basal cell carcinoma (BCC) is the most common type of skin cancer. However, it rarely metastasizes. Herein, we present a case of metastatic BCC treated with chemotherapy following vismodegib treatment failure.

Case Presentation

An 82-year-old man visited our clinic for regular follow up due to a personal history of cutaneous BCC which was located on the face. The primary tumor was excised with clear margins 16 months ago and the histopathology report indicated a nodular BCC. Physical examination revealed a swollen lymph node in the right anterior neck. The Fine Needle Aspiration of the lymph node demonstrated the presence of basosquamous BCC (BSC). Due to the presence of headaches, lacrimation and tinnitus, a head MRI and later a PET-CT scan were performed. The latter revealed bones involvement (Figure 1A). Following these findings, vismodegib treatment was initiated. A new PET-CT was performed 3 months later that indicated disease progression (Figure 1B, Figure 2A). Therefore, switch to carboplatin and paclitaxel-based chemotherapy was decided. One month after treatment initiation, the patient did not longer suffer from the symptoms mentioned above. Accordingly, three months later, a new PET-CT was performed, which revealed complete response of the BCC (Figure 2B).

Conclusions

Although BCCs are very common neoplasms, it is by nature extremely rare to metastasize.
In our patient, the primary tumor was histologically diagnosed as a nodular BCC, whilst histology of the lymph node mass indicated a BSC, which is considered a more aggressive form of BCC. This discrepancy may be attributed to sectioning limitations, not always allowing examination of all the areas of the tumor, in conjunction with the possible coexistence of different areas of differentiation within the tumor mass. Mixed histology is a common scenario, especially in large BCCs. Recent introduction of line-field confocal optical coherence tomography for the in-vivo diagnosis of keratinocyte tumors has improved BCC subtype recognition and its aggressive variants like basosquamous carcinoma. Thus, it could serve as a very helpful tool for clinicians even in such cases to overcome this discrepancy [1,2].

Surgical excision with clear margins is the gold standard of treatment of all BCCs. In contrast, in locally advanced and metastatic BCCs the therapeutic management seems to be limited to the so-called sonic hedgehog pathway inhibitors (HHI), namely vismodegib and sonidegib. However, their use remains controversial in the case of BSCs. Specifically, several studies in the past demonstrated squamatization of BCC in the setting of acquired drug resistance during HHI therapy [3,4]. On the other hand, recent studies have reported complete responses of locally advanced BSCs with vismodegib [5]. In

Figure 1. Metastatic BCC. (A) PET-CT at baseline displaying bone involvement and a mass of soft tissue in the skull base invading the clivus, both petrosal bones and the right sphenoid bone. An additional mass of soft tissue is seen to protrude back of the right sphenoid bone to the right sinus. (B) 3 months after vismodegib administration indicating progression of the disease (black arrow).

Figure 2. Comparative PET-CTs (A) before and (B) after 3 months treatment with carboplatin combined with paclitaxel (150 mg and 120 mg were administered per week, respectively) revealing complete response and disappearance of the tumor brain metastases.
our patient, vismodegib treatment was not beneficial. However, 3-month treatment with carboplatin and paclitaxel led to radiologically confirmed, complete response of the tumor. This is in line with previous evidence suggesting that cisplatin-based chemotherapy may be associated with rapid symptomatic responses [6]. However, despite the brilliant response to the systemic therapy, long term follow-up will be of crucial importance to evaluate the real efficacy of the therapy.

This case report illustrates the clinical challenge of managing patients with metastatic BCC with squamous differentiation and, subsequently, highlights the need of a multidisciplinary approach among the clinicians involved for the patient benefit.

References


Dermoscopy and Reflectance Confocal Microscopy of Apocrine Hidrocystoma

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Key words: nivolumab, regression, melanocytic nevi, melanoma, dermoscopy


Accepted: May 30, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Hidrocystomas (AHC) are benign cystic tumors that originate from apocrine or eccrine sweat glands. While rare, apocrine AHC are typically found as solid, asymptomatic blue to black papules or nodules on the face and neck, especially around the eyelid margin. AHC arises from cystic proliferation of the apocrine gland [1], while the eccrine variant is caused by the retention of eccrine glands [2]. The etiology of apocrine AHC is largely unknown [1]. Pigmented AHC of the nasal epithelium of the eccrine origin have been reported [3], but to our knowledge, our case is one of few [4] AHC on the nasal ala reported. Additionally, we report another case of pigmented AHC and describe the reflectance confocal microscopy (RCM) findings, which are scarce in current literature [5]. Although AHC are benign lesions, based off clinical appearance alone they are often mistaken for basal cell carcinomas, blue nevi, or even melanoma. RCM can noninvasively differentiate between benign and malignant cutaneous lesions, and we review the potential application of this imaging technique in the clinical management of AHC.

Case Presentation

Case 1 is a 69-year-old male with Fitzpatrick Skin type III presented with concerns for a 2-mm homogenous, well demarcated blue-gray papule on a background of sun-damaged hyperpigmented skin (Figure 1, A and B). Initial clinical assessment was determined as a blue nevus potentially superimposed upon a solar lentigo, and a shave biopsy was done to rule out malignant melanoma given the patient reported history of excessive sun exposure and rapid growth of the lesion. The specimen routinely stained with hematoxylin and eosin and histologically diagnosed as a pigmented AHC. Microscopic examination revealed a cystic structure containing focal granular pigmented material whose upper portion was lined by cuboidal epithelial cells. The lesion was histologically diagnosed as a pigmented AHC. The specimen
routinely stained with hematoxylin and eosin and histologically diagnosed as a pigmented AHC (Figure 1C).

Case 2 is a 63-year-old male presented with a history of non-melanoma skin cancer who presented with concerns for an asymptomatic lesion located on his central forehead. The patient reported that the lesion has been present for an unknown amount of time but has recently grown in size over the last few months. Clinical and dermoscopic examination revealed a well demarcated 4-mm blue homogenous papule (Figure 2, A and B). The lesion was further evaluated with RCM (Vivascope 1500) which revealed a normal honey-combed epidermal architecture surrounding a hypo reflective space. Deeper images reveal dark lacunae near normal adnexal structures (Figure 3A), representative of cystic spaces. These findings along with the absence of concerning features such as pagetoid cells or non-edged papillae favored diagnosis of a benign AHC. However, due to patient concern for the growing lesion, the lesion was removed using a shave biopsy technique and histopathological assessment illustrated a cystic space lined by several layers of cuboidal epithelial cells, confirming the diagnosis of pigmented AHC (Figure 3B).
Conclusions

This paper reports a unique anatomical presentation of an apocrine variant of pigmented AHC and discusses the differential diagnosis of pigmented papules or nodules on the body, specifically blue nevi and melanoma. AHC can grossly present as a blue papule or nodule that can be mistakenly clinically diagnosed as a blue nevus, pigmented basal cell carcinoma (BCC), or even melanoma. While AHCs and blue nevi are benign, skin cancers like BCC and melanoma have malignant potential, thus histologic evaluation can be of benefit. Blue nevus-like melanomas have two reported pathogenesis: melanoma arising coincidentally with a benign blue nevus or arising de novo and mimicking a blue nevus [6]. While rare, it is important to note an initially benign blue nevus also has the potential to become malignant [7-9]. AHC may be benign, however it is important to be familiar of other malignancies with similar clinical presentations as potential differential diagnosis.

Familiarity with features of AHC may promote accurate clinical diagnosis and avoid the unnecessary financial, cosmetic, and psychological implications associated with physical biopsies. AHC tend to appear as a solitary, homogeneous papule or nodule, typically ranging in size from 3-15mm [10], either skin-colored or with pink, yellow or blue color hue, and can have secondary features such as arborizing vessels seen under dermoscopy [11]. AHC most commonly appears on the eyelid margins [12-15], oral mucosa [16,11,17] and ear [11,17,18]. We would like to report that both our cases of AHC, when compared to more classical presentations, do not have arborizing vessels, and has a less common location on the nasal ala, contributing to the literature of other variants, including eccrine [19] and planar AHC variants [20], reported on the nasal ala.

It is important to utilize advanced imaging technologies to discern differential diagnosis of blue skin lesions with malignant potential, such as blue nevi, BCC, and melanoma from a completely benign entity like hidrocystoma. Recognizing the absence of certain features of BCC such as bright tumor islands with abundant vasculature and pleomorphism of the overlying epidermis [21-24] or features like nucleated round, dendritic, or spindled cells and non-edged papillae which can be found in melanocytic lesions with malignant potential like blue nevi or melanoma [25] can provide clinicians with enough confidence to safely monitor the lesion without sampling. The clinical benefits of utilizing RCM include prevention of unnecessary biopsies, decreased pain, improved cosmetic outcomes, and enhanced surveillance for recurrent malignancy [26]. Data on RCM characteristic findings for hidrocystomas is scarce in current literature [4,22] and we provide further evidence supporting the features of hidrocystoma commonly seen on RCM including homogenous cystic structures adjacent to normal appearing adnexal structures.

The variations and overlapping features in the clinical presentation of AHC, blue nevus, melanoma and non-melanoma skin cancer may make it challenging to dictate appropriate management therefore, it is important to consider the diagnosis of pigmented AHC clinically when there is a suspicion of blue nevus, BCC, or melanoma. Dermoscopic and reflectance confocal microscopic assessment of the lesion aids in an accurate diagnosis which may to guide appropriate patient care.

Figure 2. (A) Clinical image of a single darkly pigmented papule located on the central forehead. (B) Dermoscopy image demonstrating a 4-mm blue-violet homogenous well-demarcated papule.
Figure 3. (A) Reflectance confocal microscopic image of the superficial dermis reveals adnexal structures (yellow star) surrounded by several hypoechoic lacunae (yellow arrows) representative of cystic spaces. (B) Histopathologic image showing a cystic lumen with the upper portion demonstrating an attenuated lining containing 2 layers of flattened to cuboidal epithelial cells (arrows) and pigmented brown granular material (star) in the cystic space (H&E, x100).
References


Dermoscopic Features of External Ear Melanoma: A Case Series

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Key words: Melanoma, dermoscopy, ear


Accepted: June 1, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

External ear melanoma (EEM) is a rare condition, corresponding to 1%-4% of all cutaneous melanomas. It affects mainly individuals in the sixth decade of life, being predominantly observed in white men, in the auricular helix. The most common subtype that have been reported is the superficial spreading melanoma (40.1%), followed by the lentigo maligna (33.7%) [1]. EEM usually exhibits the classical features of facial or extra-facial melanoma, both clinically and dermoscopically [2]. The majority of these melanomas are diagnosed in early stages, when the Breslow thickness is less than 2 mm, in 75% of patients [1]. We report eight clinical cases of EEM and their dermoscopic findings, diagnosed at an early stage, emphasizing the importance of the routine clinical examination of the ears in the dermatological consultation.

Case Presentation

Eight patients (7 men and 1 woman) with biopsy-proven diagnosis of melanoma were analyzed. The median age was 68 years (range, 54–82 years). Two were located on the right helix, 3 on the left helix, 1 on the right lobe, 1 on the left antihelix and 1 on the left antitragus. All of them presented as a single lesion and only two patients noticed its appearance before consultation. Clinically, they were pigmented brown macules, with the exception of one that presented as a multicolored, slightly raised lesion. Most of them showed asymmetrical shape. Upon dermoscopy, in 6 out of 8 lesions, we found features of lentigo maligna, such as asymmetric pigmented follicular openings, rhomboidal structures and dark brown homogeneous areas without obliterated hair follicles (Figure 1, A-F), 1 lesion presented dark brown homogeneous areas with obliterated hair follicles (Figure 1G) and 1 exhibited criteria for superficial
Figure 1. Clinical and dermoscopic images of external ear melanomas. Dermoscopic examination developed. (A,B) Asymmetric pigmented follicular openings, and concentric circles. (B) Zig-zag pattern (black arrows) and some rhomboidal structures (black asterisk). (C) Annular-granular pattern. (D,E) Rhomboidal structures. (F) Dark brown homogeneous areas without obliterated hair follicles. (G) Dark brown homogeneous areas with obliterated hair follicles. (H) Multicomponent pattern with multiple colors, atypical pigment network, negative network, irregular blotches and dotted and linear irregular vessels distributed peripherally (white arrow).

Conclusions
In the dermoscopic findings of this EEM case series we achieved similar results to those in previous reports, showing classical dermoscopic features of facial and extra-facial melanomas.
Face-specific dermoscopic criteria of melanoma are asymmetric pigmented follicular openings, concentric circles, annular-granular pattern, rhomboidal structures, and homogeneous areas. Extra facial melanoma features in general include atypical pigment network, angulated lines, irregular dots and/ or globules, irregular streaks/ pseudopods, irregular blotches, regression structures, blue-white veil, negative network, shiny white structures, milky-red areas, and atypical vascular pattern [3]. Concerning melanoma subtype, unlike previous reports, lentigo maligna was more frequent than superficial spreading melanoma in our series. 6 out of 8 cases were melanomas in situ, the other 2 were invasive melanomas (Breslow thickness 0.6 and 1.2 mm, respectively).

To conclude, the importance of routine clinical examination of the ears during dermatological consultations is reinforced, recommending the use of the dermatoscope when evaluating single lesions in this location, in order to recognize an early melanoma. Early diagnosis of EEM directly impacts on survival and dermoscopy has been shown to aid in the correct diagnosis.

### References


Introduction

Pigmented Bowen disease (pBD) is a rare variant of squamous cell carcinoma in situ of the skin. Precise diagnosis of pBD can be difficult based only on clinical and dermatoscopic findings. Reflectance confocal microscopy (RCM) plays an important role by showing atypical keratinocytes and full thickness atypia in vivo. Previous studies showed confounding presence of hyper-refractile elongated dendritic cells in pigmented actinic keratosis (AK)/pBD on RCM [1].

We present a case of pBD located on the facial skin misdiagnosed as lentigo maligna with RCM due to the presence of abundant hyper-refractile, atypical dendritic cells in the interfollicular spaces.

Case Presentation

A 73-year-old female with skin type II was seen for a 5 mm pigmented lesion on the right cheek (Figure 1A). Dermatoscopic examination showed an asymmetrical pigmented lesion with multiple colors, pigmented circles, and dotted and fine linear vessels on an erythematous background (Figure 1B). RCM images at the spinous and supra-papillary/basal layer showed an atypical honeycomb (Figure 1, C and D) pattern and numerous bright edged papillae (Figure 1E) and dispersed bright fusiform and stellate shaped cells with thin dendrites (Figure 1F). A complete surgical excision of the lesion was performed with 2 mm of tumor-free margins. Histopathology revealed a pBD including full thickness keratinocytic atypia, prominent basal layer pigmentation,
and dermal melanophages (Figure 2). The patient continues routine care via skin cancer surveillance.

Conclusions

The diagnosis of pBD can be challenging clinically due to relative rarity and various clinical presentations. Dermatoscopy can be a helpful tool in diagnosing these lesions [2]. However, in equivocal cases, RCM plays an important role in differentiating pBD from lentigo maligna (LM). Typical RCM features of BD are full thickness keratinocytic atypia and architectural disorganization of the epidermis which presents as atypical or disarranged honeycomb pattern. Recent studies highlighted that intraepidermal dendritic cells can be found in pigmented AK/pBD which creates a potential diagnostic pitfall. Moscarella et al reported dendritic cells in 12/17 cases of AK/BD [3]. Persechino et al found bright interfollicular dendritic cells in 53% of AK cases [4]. RCM features of LM includes atypical melanocytes and nests surrounding adnexal openings, sheets of cells composed of mainly dendritic cells giving a ‘medusa head’ appearance at dermo-epidermal junction (DEJ). Folliculotropism is a typical feature of LM and is visualized as dendritic, atypical cells infiltrate the follicles [4]. Thus, it is important to visualize

Figure 1. (A) Clinical examination of the lesion on the right preauricular area shows a 5 mm diameter asymmetrical pigmented. (B) Dermatoscopy reveals an asymmetrical pigmented lesion with multiple colors, pigmented circles, dotted and fine linear vessels on an erythematous background. (C) RCM images at the spinous and suprapapillary/basal layer shows an atypical honeycomb pattern and numerous bright edged papillae. (D) Higher magnification of atypical honeycomb pattern adjacent to the lesion which is highlighted with red bracket in (C). (E) Higher magnification of bright ringed-edged papillae at the level of dermo-epidermal junction shown with yellow arrow in (C). (F) Higher magnification of dendritic cells between ringed edged papillae (this image is obtained with VivaStack mode).

Figure 2. Histologic examination shows full thickness keratinocyte atypia, disorganization of the keratinocyte and prominent basal layer pigmentation with dermal melanophages.
DEJ in detail and follicular structures for signs of dendritic cell infiltration to rule out LM. Other clues for pBD are numerous marked small bright rings at DEJ [5,6]. Since DEJ is infiltrated by malignant melanocytes in LM, presence of regularly shaped bright rims can signify pigmented AK/pBD.

Intraepithelial hyper-reflective dendritic cells are found quite high in pBD. The exact nature of these cells is unknown, and density of dendritic cells can correlate with clinical pigmentation of the lesion. Thus, it is imperative to be aware of the presence of dendritic cells. In the presence of dendritic cells in a pigmented lesion should not prompt extensive surgical excision without the evidence of melanocytic neoplasm. In doubt, incisional biopsy of the lesion should be considered to avoid extensive surgical treatment. Thus, RCM plays a critical role for the management of facial pigmented lesions in aesthetically sensitive sites.

References
Two New Dermoscopic Features of Trichostasis Spinulosa and Its Reflectance Confocal Microscopic Appearance

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Key words: Trichostasis spinulosa, dermoscopy, reflectance confocal microscopy


Accepted: April 7, 2022; Published: January 2023

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Trichostasis spinulosa (TS) is a relatively common yet unrecognized follicular disorder characterized by the retention of numerous vellus hairs surrounded by a hyperkeratotic dilated hair follicle [1]. The main dermoscopic structures of TS have been identified previously [2]. Herein, we identify two new dermoscopic features of TS and report its reflectance confocal microscopy (RCM) characteristics for the first time.

Case Presentation

A 25-year-old woman complained of progressive multiple, black-colored keratotic lesions with mild pruritus involving her trunk for 2 years. Her medical history was otherwise unremarkable. Physical examination revealed numerous black, firm, discrete, 0.2-0.5 mm follicular keratotic papules on the abdomen and back (Figure 1, A and B). Histopathology revealed hyperkeratosis with follicular plugging, a dilated infundibulum containing multiple vellus hairs enveloped in keratinous material (Figure 1C). The microscopic examination illustrated a cluster of vellus hairs embedded in keratinous material from an extracted plug (Figure 1D). Dermoscopy demonstrated a bundle of vellus hairs projecting together (Figure 2A) and keratotic plugs in some dilated follicles. In addition, dark concentric hair forming a circle under the horny layer (circle hair) and hairs rolled in spiral with peripilar casts (rolled hair) were also seen (Figure 2, B and C). RCM showed dilated follicular openings were consisted of moderate-refractive keratotic substitutes and/or hyper-refractive numerous vellus hairs (Figure 2, D and E). Based on the above findings, the diagnosis was consistent with TS.
Conclusions

Two clinical variants of TS have been proposed, namely non-pruritic and pruritic type [3]. We present a patient classified as pruritic type which usually affects young adult characterized by multiple itchy follicular papules mainly on the trunk and upper limbs. The diagnosis of TS is usually based on clinical presentation, microscopy and sometimes on histopathology. However, dermoscopy is the most helpful tool in clinical practice. The main dermoscopic characteristics of TS, including tufts of short, vellus hairs emerging together and keratotic plugs of some follicular openings, were noticed in our patient as previously described [2]. Furthermore, we observed two new dermoscopic findings of TS: circle hair and rolled hair. Circle hair is almost exclusively found incidentally on the trunk and upper legs of overweight men, where they are interspersed with normal hairs [4]. Rolled hair is associated with many conditions such as ichthyosis, keratosis pilaris, xerosis, neurodermatitis, and palmoplantar keratoderma [5]. Some authors attributed rolled hair to mechanical trauma resulting from repeated and vigorous rubbing.

RCM is a high-resolution imaging technique which allows in vivo visualization of upper layers of skin structures. However, the RCM characteristics of TS have not been described so far. In this study, we observed RCM features as moderate-refractive and hyper-refractive structures among
Figure 2. (A–C) Dermoscopy demonstrated tufts hairs (black arrows), rolled hairs (red arrows), circle hairs (blue arrows), and blackhead-like structures (yellow arrows) (x10). (D–E) Reflectance confocal microscopy illustrated an oval-shaped moderate-refractive structure (red arrows) in the epidermis and hyper-refractive piliform structures (blue arrows) among dilated follicular openings (basic image, 0.5mm × 0.5mm).
dilated follicular openings, corresponding well to histologic horny follicular plugs and tufts vellus hairs, respectively.

In conclusion, we have proposed two new dermoscopic signs of TS and its RCM features. These techniques, combined with the clinical findings, may be useful to diagnosis of TS, possibly limiting the need for skin biopsy.

References
Dermal Amyloid Deposits: A Possible Misleading Pathologic Finding

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Key words: amyloid deposits, drug eruption, systemic amyloidosis, cutaneous involvement


Accepted: May 9, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Amyloid is a highly organized fibrillar substance resistant to macrophage degradation. It can originate from more than 27 misfolded proteins. Extracellular amyloid deposition may result from several pathophysiological processes: abnormal protein production, excessive presence of normal proteins or senescence. Recently, reclassification of amyloidosis based on protein type led to the identification of subgroups with different etiology (acquired or inherited), clinical manifestations, and prognosis [1]. Some forms are localized while others involve multiple organs. Dermal amyloid deposits can be detected in both cases. Cutaneous localized amyloidosis includes keratinic and nodular amyloidosis. In the first case the macular and lichenoid lesions correspond to subtle deposits limited to the upper dermis, in the second case plaque and nodules are secondary to deep dermal and subcutis deposits.

The spectrum of cutaneous involvement in systemic amyloidosis encompasses a wide variety of lesions that reflect localization and abundance of amyloid deposits. Generally, amyloid deposition affects dermal blood vessels, that easily rupture upon minimal trauma, with subsequent appearance of petechiae, purpura and ecchymoses, mostly located on body folds. Profuse infiltration of amyloid within the dermis and the subcutis can manifest also as papules, plaques, nodules, bullae, and even scleroderma-like lesions. Amyloid infiltration in or about sweat glands, sebaceous glands, and hair follicles can result in anhidrosis and alopecia [2]. Curiously, amyloid deposits have been demonstrated in all of the aforementioned sites, also in clinically uninvolved skin [3]. Here, we present a case of massive dermal amyloid deposit both in involved and uninvolved skin that mislead clinical diagnosis.

Case Presentation

A 53-year-old man presented with a pruritic, non-confluent, maculopapular eruption of one month duration, consisting of discrete 5-10 mm lesions, symmetrically distributed on his
trunk, arms and upper thighs (Figure 1). His medical history was significant for multiple myeloma and systemic amyloid light-chain (AL) amyloidosis with cardiac, gastric and bone marrow involvement. He had been treated with allogenic bone marrow transplantation followed by bortezomib, endoxaban and dexamethasone without any adverse cutaneous reaction. The patient received pomalidomide ten days before the onset of the rash and the drug was promptly discontinued. He complained of xerostomia and development of hematomas after mild trauma. Histological examination revealed presence of multiple hyaline deposits in the superficial dermis, with perivascular, peri-adnexal, and interstitial arrangement (Figure 2A). Congo-red staining positivity along with apple-green birefringence under polarized light was consistent with amyloid (Figure 2B). Immunohistochemical typing of amyloid revealed lambda light chain accumulation (Figure 2C).

A course with prednisone 25 mg daily tapered over three weeks quickly led to clinical resolution of the eruption. However, 3 days following pomalidomide reintroduction, sudden reappearance of the same monomorphous lesions was observed.

Two additional punch biopsies were performed, on lesional and non-lesional areas, respectively. The former showed diffuse vacuolar change in the basal layer of the epidermis with scattered necrotic keratinocytes and a band-like superficial inflammatory infiltration. Amyloid deposits were detected in both specimens. Finally, a diagnosis of lichenoid drug eruption in the setting of systemic AL amyloidosis with concomitant massive dermal amyloid deposits was made.

Conclusions

Globally, mucocutaneous lesions have been described in 30% of all cases of systemic amyloidosis, and in up to 50% those with AL type [4]. Although the dermatologist may have a crucial role in the prompt diagnosis of systemic amyloidosis [5], massive presence of cutaneous amyloid, as in our case, could mislead both the dermatologist and the pathologist involved in the diagnostic process, masking other concurrent disorders. Indeed, detection of amyloid deposits in normal-appearing skin has been widely demonstrated in literature: in the past, several studies proposed to perform biopsy on uninvolved skin to confirm systemic cases.

Figure 1. Non-confluent, maculopapular eruption of discrete 5-10 mm lesions on patient lower back (A), right arm (B) and right forearm (C).

Figure 2. Histopathology showing diffuse vacuolar change in the basal layer of the epidermis with scattered necrotic keratinocytes and a band-like superficial inflammatory infiltration. (A) H&E x200 Notice dermal amyloid deposit (black arrows). (B) Congo red stain highlighting dermal perivascular, peri-adnexal, and interstitial infiltration of amyloid. (C) Immunohistochemical typing of amyloid revealing lambda light chain accumulation.
of amyloidosis [3]. However, even if type of dermatological findings depends on amyloid localization, the exact amount of deposit capable to trigger clinical modification has not yet been identified. In systemic amiloidosis, the presence of deposits in uninvolved sites enforces the idea that detection of amyloid in cutaneous lesions should not lead to hasty diagnostic conclusions. Although the possible cutaneous manifestations of systemic amyloidosis are protean, clinical confirmation bias should always be considered and avoided.

References


Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a potentially curative treatment in patients with mycosis fungoides (MF) and may be used in selected patients with advanced disease [1]. The differentiation of MF relapse from other skin diseases that occur after transplantation is challenging. In this case series we present the dermoscopic observation of MF lesions after alloHSCT.

Case Presentation

We have performed a dermoscopic follow-up of MF skin lesions in 3 patients before and after alloHSCT. Dermoscopic images were captured using the DermLite Cam with polarized light and independently analyzed by two certified dermoscopists (G.K-W, A.SZ-S), blinded to the clinical status of the disease. The progression was determined as new MF lesions were confirmed in the histopathologic examination.

The details of the disease, alloHSCT procedure and dermoscopic assessment are presented in Table 1. Treatment was tolerated well, and there was no case of transplant-related mortality.

In active MF, red and orange color of the background was found with the presence of numerous dotted and/or linear vessels, distributed unspecifically, uniformly, or in clusters. In one case increased white and yellow scaling was noted in patchy distribution. In cases of disease regression, a visible change in background color was noted (from red to skin-colored or light brown) (2/3), with the disappearance of the previously described vessels.
Table 1. Dermoscopic assessment of skin lesions in the course of allogeneic hematopoietic stem cell transplantation for mycosis fungoides.

<table>
<thead>
<tr>
<th>Patient case number; Gender</th>
<th>Conditioning regimen; Donor; Immunosuppression</th>
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<td>1; M</td>
<td>Fludarabine+ Melphalan; MUD; CsA+Mtx</td>
<td>PR, then PD (treated with DLI), then PR (5,5 years)</td>
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<tr>
<td>2; F</td>
<td>TSI+TLI+ATG; MUD; CsA+MMF</td>
<td>CR (3 years)</td>
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<tr>
<td>3; F</td>
<td>Fludarabine+TBI; MUD; CsA</td>
<td>PD (100 days)</td>
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<th>+14</th>
<th>+41</th>
<th>+696</th>
<th>-1</th>
<th>+14</th>
<th>+27</th>
<th>+87</th>
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<th>+14</th>
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<th>brown parallel lines</th>
<th>grey dots and globules; white angulated lines</th>
<th>grey dots and globules; white angulated lines</th>
<th>white diffuse structureless areas; grey dots and globules</th>
<th>white diffuse structureless areas; brown dots and globules</th>
<th>white focal structureless areas; brown lines</th>
<th>white focal structureless areas; brown focal globules</th>
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<tr>
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<th>uniform dotted</th>
<th>uniform dotted</th>
<th>peripheral dotted</th>
<th>unspecific linear</th>
<th>unspecific linear</th>
<th>unspecific linear</th>
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<th>orange (salmon)</th>
<th>light brown</th>
<th>skin-colored</th>
<th>skin-colored</th>
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<th>skin-colored</th>
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Abbreviations: alloHSCT- allogeneic hematopoietic stem cell transplantation; ATG- antithymoglobulin; CsA- cyclosporine A; CR- complete remission; DLI- donor lymphocyte infusion; F- female; M- male; MMF- mycophenolate mofetil; Mtx- methotrexate; no- number; MUD- matched unrelated donor; PD- progressive disease; PR- partial remission TBI- total body irradiation; TLI- total lymphatic irradiation; TSI- total skin irradiation.
Dermoscopy in the setting of alloHSCT may help to differentiate between a variety of skin conditions after the procedure, including relapse of the primary disease, cutaneous graft versus host disease, drug-induced rashes, infectious skin disorders, and secondary cutaneous neoplasms. Dermoscopy is an auxiliary tool in the differentiation of inflammatory disorders and MF based on the vessels’ morphology and their distribution, color of the background, color and distribution of the scales [2].

Dermoscopic features of MF described in the literature include short linear and dotted vessels [3,4,5,6] and spermatozoa-like vascular structures [3,4,5].

In our cohort, both dotted and linear vessels were noted, and they were indicative of an active disease process.

Background color in MF is red, yellow-orange [5] or a mix of the two colors [2]. The primary red or orange background color, changing to skin-colored or light brown in the case of healing of the lesions was also noted in our patients. The presence of scale seems to be not specific in the dermoscopy of mycosis fungoides. The large variation in descriptions of its presence and distribution [2,4,6] may be due to the use of a dermoscope with non-polarized light requiring immersion vs. polarized light, where scale is more easily visualized [2]. In our group, scaling was reported in active lesions.

Other noted structures such as white diffuse structureless areas, brown lines and globules were present irrespective of disease status.
Conclusion

Our report adds to the information about the dermoscopic characteristics of MF lesions and their evolution. Observations in the case of disease remission included a change of the background color from initial red-orange to skin-colored or light brown and the disappearance of numerous dotted and linear vessels, while the persistence of vessels was indicative of progressive disease.

References


Basal Cell Carcinomas Presenting as Flat Pigmented Macules on the Face Mimicking Lentigo Maligna on Dermoscopy: A Case Series.

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Key words: dermoscopy, dermatoscopy, basal cell carcinoma, lentigo maligna, melanoma, face


Accepted: April 24, 2022; Published: January 2023

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Basal cell carcinoma (BCC), the most common type of skin cancer, can usually be diagnosed with dermoscopy with high accuracy [1]. We noted, however, that certain pigmented BCCs (pBCCs) are more difficult to diagnose than others. These challenging pBCCs usually appear as flat, pigmented lesions on the face and mimic lentigo maligna (LM). To better characterize these types of pBCCs, we retrospectively collected typical cases of this clinical presentation and re-evaluated the dermoscopic findings.

Case Presentation

Cases were selected retrospectively from databases from Austria, Chile, and the United States. Cases were included if they were clinically pigmented and flat. Most cases were submitted for biopsy with LM in the differential diagnosis. We analyzed both pBCC and LM dermoscopic criteria by two independent investigators (CND and HK). A third reviewer helped solving disagreements (PU or AA). For reflectance confocal microscopy (RCM) images, we used a wide-probe RCM (Vivascope 1500). Biopsy reports were obtained from clinical records and reviewed by expert dermatopathologists. Finally, we analyzed the dermoscopic images with a previously validated convolutional neural network (CNN) (https://dermonaut.meduniwien.ac.at/ypsono) and recorded the top-1 and top-3 accuracy rates [2].

We found 10 cases of BCCs that mimicked LMs. The mean age at diagnosis was 73 years (range: 44-87 years) and 6 of the 10 patients were females. All BCCs presented as flat pigmented macules on sun-exposed areas of the face...
(Table 1). On dermoscopy, the main feature was a pattern of angulated lines without obliteration of the follicular openings, in all cases (Figure 1 and 2). This pattern mimicked the rhomboidal or ‘zig-zag’ pattern of LM. Additionally, all cases had pink areas and lacked the typical vascular pattern of BCC. Shiny white blotches and strands were seen in 4 out of 10 (40%). One case was examined by RCM and showed classic BCC features such as tumor nodules and cords with

<table>
<thead>
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<th>Gender</th>
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<td>Superficial</td>
<td>Nose</td>
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<td>M</td>
<td>Superficial</td>
<td>Forehead</td>
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<td>Nose</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>M</td>
<td>Superficial</td>
<td>Forehead</td>
</tr>
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<td>M</td>
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<tr>
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<td>87</td>
<td>F</td>
<td>Superficial and nodular</td>
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</tr>
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<td>8</td>
<td>77</td>
<td>F</td>
<td>Superficial and nodular</td>
<td>Forehead</td>
</tr>
<tr>
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<td>83</td>
<td>F</td>
<td>Nodular, multifocal</td>
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</tr>
<tr>
<td>10</td>
<td>42</td>
<td>M</td>
<td>Superficial</td>
<td>Cheek</td>
</tr>
</tbody>
</table>

M = male; F = female.

**Figure 1.** Basal cell carcinoma presenting as flat pigmented macules. (A) Clinical features of a flat pigmented macule on the nasal supratip. (B) Dermoscopic features showing rhomboidal structures (arrow) and a pink background (asterisk) (polarized light dermoscopy, original magnification x10). Inset shows reflectance confocal microscopy features showing tumor nodules with palisading and clefting (original magnification x30). (C) Clinical features of a flat pigmented macule on the right cheek. (D) Dermoscopic features showing rhomboidal structures (arrow), pink background, and shiny white blotches and strands (asterisk) (polarized light dermoscopy, original magnification x10).
Figure 2. Basal cell carcinoma presenting as flat pigmented macules. (A) Clinical features of a flat pigmented macule on the right nasal tip. (B) Dermoscopic features showing rhomboidal structures (black arrow) and a pink background with shiny white blotches and strands (asterisk) (Polarized light dermoscopy, original magnification x10). (C) Clinical features of a flat pigmented macule on the left nasal tip. D. Dermoscopic features showing rhomboidal structures (black arrow) and a pink background (asterisk) (Polarized light dermoscopy, original magnification x10).

Conclusions

We characterized a previously undescribed presentation of facial pBCCs mimicking LM. The common confounding feature seen in all cases was angulated lines (ie ‘rhomboidal’, ‘zig-zag’) without involvement of hair follicles. Although all cases were typified by pink structureless areas, none displayed the typical serpentine and branching vessels of BCC. In our experience, LM only rarely displays pink areas, which could be a clue for the correct diagnosis of BCC. Shiny white blotches and strands also rarely appear on LMs [3]. The poor performance of a previously validated CNN underlines that these pBCCs are difficult to diagnose [2]. Limitations of this study are (1) that we were not able to estimate the frequency of this type of pBCC in clinical practice, (2) that we did not include a control group of other flat pigmented lesions such as pAK or LM, which is the main mimicker, (3) cases were not consecutive and there might be selection and recall bias, (4) no histopathological correlation of the angulated lines in BCCs was available, and (5) no pathology slides review was performed for BCC histopathological subtypes; however, all cases were initially signed by expert dermatopathologists.

In summary, when evaluating flat pigmented lesions on the face, pBCC should be included in the differential diagnosis [4]; especially when seeing angulated lines amidst pink areas with or without shiny white blotches and strands.

References


Lichen Striatus Post-COVID-19 Infection: Clinical and Dermoscopic Presentations

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Key words: Lichen striatus, COVID-19, infection, rash


Accepted: April 23, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 24-year-old female with classic symptoms for COVID-19 underwent a rhino-pharyngeal swab test in October 2020 that confirmed the infection. She had been previously vaccinated with two Pfitzer vaccine doses in July. Nine days after the positive rhino-pharyngeal swab test, the patient came in consultation with small, 1-2 mm elevated pinkish papules that joined together in a slightly scaly, irregular, linear band of about 20 cm following Blaschko lines on the medial portion of the left leg (Figure 1, A and B). The patient reported that the rash had appeared 2 days after COVID-19 symptoms started and that it caused her moderate pruritus. Dermoscopy showed a slight erythematous pinkish background and confluent areas of telangiectatic vessels, ruling out other diseases (eg ILVEN, linear psoriasis or linear Darier disease) (Figure 1, C and D). A 4-mm punch confirmed the clinical suspicion of LS. LS has a self-limiting nature, with an expected complete recovery. However, because this patient sought treatment, a short course of topical steroids together with antihistamines were prescribed to treat the itch and dryness of the skin. After 6 weeks the patient had no more signs of active disease, and no post-inflammatory hypopigmentation was observed. Usually relapses of this condition are uncommon.

Teaching Point

Few papers have reported LS after COVID-19 vaccination [1], but this case shows that also COVID-19 infection could be a trigger, although pathophysiological mechanisms and causes underlying this condition are still not completely understood.

Being a benign self-limiting condition, usually no treatment is required, although low doses of systemic corticosteroids or topical corticosteroids can contribute to provide some benefits in symptomatic patients [2].
References


To the Editor,

Lentigo maligna (LM) represents the most common subtype of melanoma in the elderly, affecting predominantly the head and neck region in photodamaged patients. Surgery with 5 mm margins is the treatment of choice but patient comorbidities, impact of surgery intervention and the reduction of quality of life resulting from surgery can limit its application. In situations for which surgery would have a major impact on the functionality of the anatomic region or would result in cosmetically devastating outcome, radiotherapy or imiquimod (IMQ) represent valid alternatives. IMQ could cause significant skin reactions and little is currently known on its impact of the eye if applied in the periorbital region. Herein, we report the case of a 74-year-old woman, referred to our skin cancer department for a brownish macule located on left lower eyelid. Previous history revealed the excision with 5 mm margins of a LM 4-years before. A first recurrence appeared two years later and was surgically treated.

At current visit, a brownish macule of about 6-mm located on the lower eyelid was observed (Figure 1A). Dermoscopic evaluation showed a brown pseudo-network with intense pigmentation and obliterations of follicles (Figure 1B). A 4mm punch biopsy was performed, confirming the dermoscopic diagnosis of lentigo melanoma. The patient was discussed in our multidisciplinary tumor board because surgery would have an impact on the functionality of the eye and also because the patient refused further surgery. Based on the data suggesting a good response of LM to topical treatment with IMQ 5%, it was started five days per week. Considering the tumor closeness to conjunctiva and cornea and the risk of occasional applications of the drug in the eye during the treatment, a close dermatological and ophthalmological evaluations were performed every two weeks. After 4 weeks a partial response was observed (Figure 1, C and D) and after 6 weeks a complete response was achieved (Figure 1, E and F). At the ophthalmologic evaluation after 2 weeks of treatment, redness, burning and foreign body sensation of the conjunctivae was noted, without any decreased visual acuity. However, to limit discomfort, a combination of topical steroid and hyaluronic acid eyedrops were prescribed every day for ten days with a rapid improvement of the symptoms. Then, to prevent redness and burning sensation, hyaluronic acid eyedrops were prescribed for the entire
treatment period. At 6 months follow up visit, no clinical and dermoscopic signs of recurrence were observed and the conjunctiva did not show inflammation or impairment. The optimal response of LM to IMQ and its dermoscopic evaluation has been already proved (1,2); moreover, clinicians may be reluctant to prescribe IMQ on the eyelid because of risk of ocular adverse effects. However, O’Neill et al (3) described the case of a 52-year-old woman affected by LM, successfully treated with IMQ and, despite the patient giving a history of having applied treatment into the eye on occasion (in error) there were no adverse effects. Other reports show that the most common side effects during treatment of LM of the eyelids with IMQ are redness and burning, improved without permanent ocular damages after its discontinuation (4,5).

To prevent ocular redness and burning, the first advice to be given to patients is undoubtedly to use daily hyaluronic acid tears associated with good eyelid hygiene. In more severe scenarios, non-steroid tears should be prescribed to reduce discomfort and to increase therapeutic compliance. Therefore, considering the benefits of IMQ and the absence of permanent ocular side effects, the use of IMQ in the periocular area should not be avoided for fear of conjunctival inflammation which, if it occurs, can be treated, and prevented with topical therapy.

References


High-risk Genital-mucosal Human Papilloma Virus Types 58 and 59 Associated With Solitary Angiokeratoma on the Elbow

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Key words: Human papilloma virus 58, Human papilloma virus 59, high-risk, genital-mucosal, angiokeratoma


Accepted: April 25, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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To the Editor,

Human papilloma viruses (HPVs) are associated with a wide spectrum of cutaneous and mucosal infections and neoplasms. Though angiokeratoma can clinically mimic warts, koilocytes and presence of high-risk HPV DNA have not been reported in angiokeratoma. We describe a case of extragenital solitary angiokeratoma associated with high-risk types of HPV in a child.

A 10-year-old girl presented with two-year history of an asymptomatic bluish-black plaque on the left elbow. There was no history of preceding trauma, bleeding from the lesion or immunosuppression. Cutaneous examination revealed a well-circumscribed dark blue to black colored verrucous plaque of size 2.5 x 1.5 cm on the left elbow (Figure 1A). Dermatoscopic examination showed dark blue, violaceous and black colored round to ovoid lacunae with bluish-white veil (Figure 1B). Excisional biopsy revealed hyperkeratosis, hypergranulosis, acanthosis and papillomatosis. Numerous keratinocytes with raisinoid nuclei and perinuclear halo, characteristic of koilocytes were seen in stratum spinosum. Multiple thin-walled dilated vascular channels filled with erythrocytes were noted in papillary dermis (Figures 1C, 1D). HPV genotyping was performed with extracted DNA from biopsy tissue using Applied Biosystem 7500 Fast Dx real-time polymerase chain reaction (PCR) instrument. Target DNA was amplified for identifying either high-risk HPV (HPV types 16/18/31/33/35/39/45/51/52/56/58/59/66 and 68) or low-risk HPV genotypes (HPV 6/11) respectively. Test results identified HPV high-risk genotypes in the sample. TRUPCR high risk genotyping kit designed to qualitatively detect DNA of high-risk HPV of 14 genotypes by amplifying E6/ E7 region by primers and probes specific for the particular genotype by Real time PCR confirmed the presence of HPV-58 and HPV-59 genotypes (Cycle Threshold values 30.32 and 25.94 respectively), with a cut off value of 36 (Figures 2 A and B).
The role of HPV in the pathogenesis of non-melanoma skin cancers was initially described in epidermodysplasia verruciformis and transplant recipients. High-risk types, mainly HPV 16, are strongly linked with anogenital carcinomas and among cutaneous lesions, implicated in Bowen’s disease and squamous cell carcinoma (SCC) [1]. High-risk genital-mucosal HPV 58 and HPV 59 are risk factors for cervical carcinoma and uncommonly detected in cutaneous lesions [2-4]. HPV 58 has been identified in cutaneous premalignant and malignant lesions including, Bowen disease on the fingers and elbow, SCC and keratoacanthoma [2,3]. HPV 59 genome is most closely...
related to HPV 18, and has been reported in Bowen disease [4].

HPV infection associated with angiokeratoma has been described in a case presenting on vulva with coexisting positivity for HPV-6 [5]. High-risk genital-mucosal HPV types have not been associated with angiokeratoma. HPV proteins may promote cell proliferation through many signal transduction pathways. The reactive inflammation associated with viral infection results in tumor necrosis factor (TNF)-α production, which in turn stimulates the release of NF-κB. The latter induces production of vascular endothelial growth factor, causing vascular ectasia [6].

Our patient had angiokeratoma on elbow, without any present or past history of anogenital lesions. Interestingly, koilocytes were noted and PCR demonstrated HPV-58 and HPV-59 genotypes. The mode of acquisition of HPV infection in our case could be close contact with some family member having HPV infection. The limitation of this report is we did not assess the presence of HPV in healthy samples of perilesional and distant skin.

It remains to be determined, whether HPV merely occurs as a commensal infection due to ubiquitous presence or is related to disease pathogenesis in angiokeratoma. Nonetheless, detection of high-risk HPV types warrants close follow-up for malignant transformation.

References

To the Editor,

Chronic cutaneous lupus erythematosus (CCLE) is characterized by the presence of well-defined erythematous scaly plaques with associated atrophy, scarring, telangiectasia, and pigmentary alteration. The pigmented macular variant is a less recognized morphological variant [1].

All 3 cases in our series were female with Fitzpatrick skin phototype V. They presented with multiple, ill-defined, light-to-dark brown macules of variable size, predominantly on the face and head. Associated scarring was noticed only in Case #1. The dermoscopic feature was dominated by follicular plugging and pigment structures like brown dots, globules, homogenous areas, brown to blue-gray peppering, and brown pigment network. The brown to blue-gray peppering showed a peri-appendageal accentuation and resulted in target-like structures (central white clod/eccrine opening surrounded by brown structureless area) and perifollicular gray ring. Case-1 showed also concentric structures as dark brown clod within a light brown clod (Figure 1 and 2). The clinico-dermoscopic details of the 3 cases are given in Table 1. Two 4 mm punch biopsies were done: one for histopathological examination and the other for direct immunofluorescence from hyperpigmented macules. The histopathology of all the cases was diagnostic of CCLE. On direct immunofluorescence, linear deposition of immunoreactant IgG and, or IgM were noted along the basement membrane zone in all three cases.

George et al in 1992 reported a hyperpigmented variant of discoid lupus erythematosus and advocated that asymptomatic chronic hyperpigmented macules should alert the clinicians to suspect the diagnosis [1]. Boyd delineated...
a distinct profile of patients with solitary hyperpigmented macules over the face and neck without any scaling, atrophy, scarring, or telangiectasia [2]. These lesions had a late-onset, short disease duration, lower incidence of photosensitivity, and overall better prognosis. They could clinically be mistaken for seborrheic keratosis, solar lentigo or lentigo maligna, but the histopathology was consistent with CCLE. The three cases in our series had multiple asymptomatic light-to-dark brown macules without any previous history of inflammation and were distributed primarily on the face and around the ear.

The dermoscopic features, follicular plugging, brown to blue-gray dots, globules, or peppering in our series reflect the basic pathology of CCLE. The former corresponds to the dilated follicular infundibulum keratotic plugging, and the latter to the melanin in stratum corneum and to the dermal pigment incontinence. Besides, we observed perifollicular gray ring and peri-eccrine target-like structures, which
possibly reflected the predominance of peri-appendageal interface dermatitis and the resulting pigment incontinence [3,4]. The pigmented macular variant of CCLE will have more prominent pigment incontinence in skin of color. This feature may not be striking in Fitzpatrick skin phototype I-II.

Diagnosing the pigmented macular variant of CCLE in skin of color, as in our patients, is challenging. It can mimic various acquired hyperpigmentation disorders such as lichen planus pigmentosus (LPP), pigment contact dermatitis (PCD), and melasma. Besides, it can also be confused

Figure 2. (A) Multiple ill-defined light brown macules on the ear. (B) Dermoscopy under nonpolarized mode shows blue-gray peppering (arrow) over a light brown background. (C) Histology shows epidermal atrophy, follicular plugging, interface dermatitis, and perifollicular lymphocytes and macrophages infiltration (H & E, x100). (D) Multiple ill-defined dark-brown macules over the retro auricular area. (E) Dermoscopy under nonpolarized mode shows follicular plugging (purple arrows), pigment network (red arrow), and peppering (blue arrows). (F) Brown pigment network, follicular plugging (red arrows), and periappendageal accentuated peppering (blue arrows). (G) Focal white homogenous area with overlying peppering (arrow). (H) Histology shows atrophic epidermis along with interface dermatitis (H & E, x100). Inset shows Periodic acid–Schiff positive thick basement membrane (PAS, x400).
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we describe the clinico-dermoscopic features in three patients with skin of color. Future studies will determine the role of dermoscopy in diagnosing and differentiating this rare entity from its clinical mimics.

References


Table 1. Clinical and dermoscopic details of the pigmented macular variant of chronic cutaneous lupus erythematosus.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Gender/Age in years</th>
<th>Location</th>
<th>Duration in months</th>
<th>Associated features</th>
<th>Dermoscopic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-1</td>
<td>Female/35</td>
<td>Face, upper trunk</td>
<td>Two</td>
<td>Nil</td>
<td>Brown dots, globules, and peppering Blue-gray peppering Follicular plugging Peri-appendageal accentuation of peppering Perifollicular gray ring Target-like structures Pseudo-pigment (brown) network Concentric structures</td>
</tr>
<tr>
<td>Case-2</td>
<td>Female/30</td>
<td>Bilateral ear and infra-auricular area</td>
<td>Three</td>
<td>SLE Non-scarring alopecia ISM</td>
<td>Brown homogenous area Blue-gray peppering Follicular plugging Perifollicular gray ring</td>
</tr>
<tr>
<td>Case-3</td>
<td>Female/30</td>
<td>Bilateral ear, pre- and-post-auricular area</td>
<td>Two</td>
<td>SLE Lupus nephritis ISM</td>
<td>Brown and white homogenous area Brown and blue-gray peppering Peri-appendageal accentuation of peppering Follicular plugging Perifollicular gray ring Brown pigment network</td>
</tr>
</tbody>
</table>

SLE = Systemic lupus erythematosus.

with both benign and malignant pigment tumors such as flat seborrheic keratosis, large cell acanthoma, solar lentigo and lentigo maligna. Clinically, it may not always be possible to diagnose and differentiate pigmented macular CCLE from other causes of acquired hyperpigmentation, including post-inflammatory hyperpigmentation. Dermoscopy may help in solving this problem. Dermoscopic features described for various acquired facial pigmentary conditions in skin of color are as follows: melasma and PCD show a brown pigmentation, pseudo-pigment network, brown to gray dots and globules, and characteristically spare the peri-appendageal areas; LPP is found to have diffuse brown pigmentation, pseudo-pigment network, slate-gray to blue dots and globules, hem-like pigment pattern, and perifollicular and peri-eccrine brown to blue-gray dots. In the future, immunohistochemistry stain for melanin and/or melanocytes over a larger number of patients, as well as electron microscopy, may help to support dermatoscopy over the naked eye in the diagnosis of CCLE.

In conclusion, the clinical diagnosis of the pigmented macular variant of CCLE can be challenging due to its similarity to various facial pigmentary lesions. We describe the clinico-dermoscopic features in three patients with skin of color. Future studies will determine the role of dermoscopy in diagnosing and differentiating this rare entity from its clinical mimics.
Plica Polonica Secondary to Chemotherapeutic Drugs Combination

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Case Presentation

A 36-year-old female presented with sudden onset of matting of hair for the past three days along with non-cicatricial loss of hair from the frontal scalp and vertex (Figure 1, A and B). The patient had been on chemotherapy (cyclophosphamide and adriamycin) for the past one month for stage 4 breast cancer. The patient had proper hair care habits. There was no evidence of pediculosis capitis, psychiatric illness, or history of new shampoo use. A diagnosis of plica polonica was made based on history and examination.

Teaching Point

Plica polonica is characterized by an irreversible twisting, matting, and entanglement of hair. The exact causation and patho-mechanism of this condition are not known. Multiple factors like unkempt hair, frequent combing, use of a new or harsh shampoo, psychiatric condition, and parasitic infestation have been implicated [1,2]. Drug-induced matting of hair has been reported secondary to docetaxel, methotrexate, azathioprine, combination of paclitaxel, carboplatin, and combination of cisplatin, cyclophosphamide, doxorubicin [1,2]. Chemotherapeutic drugs disrupt the anagen phase of the hair cycle causing weakening of the partially keratinized proximal portion of the hair shaft, breakage, and shedding of anagen hair (anagen effluvium) [1,2]. The drugs can also cause cuticular damage to the proximal hair shaft predisposing to hair matting [2]. In our patient, cytotoxic agents (cyclophosphamide and adriamycin) lead to the matting of hair. The only suitable treatment for this condition is cutting matted hair or shaving [1,2].
References


Figure 1. (A) Matting of hair as seen from back. (B) Anagen effluvium over vertex of scalp.
Atypical Verrucous Presentation of Spitz Nevus

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Case Presentation

A seven-year-old girl, without any medical history, presented with a 4-year history of an asymptomatic pigmented lesion on the left ankle, which started to change and to grow - according to the family - since one year. Dermatological examination revealed a pigmented verrucous nodule of the left ankle (Figure 1A). No other lesions were found. Contact dermoscopy revealed an irregular asymmetric peripheral network, and central white globular structures surrounding violaceus vessels in some spots (Figure 1B). Spitzoid melanoma, spitz tumor or collision tumor of spitz nevus and a viral wart were discussed. The lesion was excised, histopathology revealed a papillomatous lesion with a predominance of epithelioid melanocytic cells, cellular maturation in the deep dermis, and absence of atypia or mitosis, which confirmed the diagnosis of verrucous spitz nevus, without any signs of malignancy or viral cytopathic changes (Figure 1C).

Teaching Point

Spitzoid melanocytic lesions represent a challenging spectrum from benign spitz nevi to malignant spitzoid melanoma, because of the morphological and dermoscopic overlap between them [1,2].

Spitz nevi arise more commonly in females, and in childhood but may occur at any age. There are 3 dermoscopic patterns that may be considered as suggestive of Spitz nevus: starburst pattern, regularly distributed dotted vessels and globular pattern with reticular depigmentation [2]. Although we report through this observation an atypical multicomponent pattern in a spitz nevus, excision should be performed in the case of an asymmetric lesion with a multicomponent pattern in order to rule out spitzoid melanoma.
References


An Incidental Finding of Pili-Multi Gemini of the Back

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Case Presentation

A 57-year-old man presented with a blue, pigmented patch across the left upper back. This was clinically consistent with nevus of Ito (Figure 1A). On closer inspection with dermoscopy short, dark, tufted hairs were identified which were widespread across the entire back. Multiple hairs measuring < 1 mm arose from each follicular opening (Figure 1B). This finding was isolated to the back. There was no history of prior hair removal to otherwise explain this appearance. A clinical diagnosis of widespread pili multigemini was made.

Skin punch biopsy was performed which confirmed the clinical diagnosis. Treatment was not indicated as the patient was asymptomatic at time of diagnosis.

Teaching Point

Pili multigemini is an unusual hair follicle dysplasia, characterized by clusters of shafts that emerge from a single follicle. Folliculitis may also be present. Diagnosis is clinical. Dermoscopy or trichoscopy is helpful for visualizing multiple hairs emerging from the same follicular opening. Electron microscopy shows multiple distorted hair shafts within a common root sheath. Treatment with permanent, laser ablative techniques can be considered for cosmesis. It is rarely described in the literature due to under-reporting in clinical practice and is most commonly found in male facial hair [1,2].

Dermatologists should be vigilant for pathology that may be hidden within concomitant skin changes and this case
emphasizes the importance of thorough full skin examination enhanced by the use of dermoscopy. It raises the discussion of whether pili multigemini represents a true, rare phenomenon or underdiagnosis due to its asymptomatic nature.

References


Figure 1. (A) 15 cm blue pigmented patch distributed across the left upper back with visible widespread dark, follicular changes. (B) Dermoscopy demonstrating multiple 0.5mm-1mm tufted hairs arising from within each follicular opening.
Dermoscopic Features of Pigmented Mammary Paget Disease

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Case Presentation

A 69-year-old, Hispanic woman presented with a 6-month history of an irregular, asymmetrical, dark brown lesion on the left nipple, surrounded by a discrete pink plaque (Figure 1A). Dermoscopic examination showed an atypical pigment network, black granules and globules at the center of the lesion, as well as structureless pink and white areas (Figure 1B). Histopathology revealed epidermal infiltration by large, atypical, pale cells. Immunohistochemistry was negative for negative for s100, Melan-A, and HMB-45, hence ruling out the presumptive diagnosis of malignant melanoma. Immunohistochemical staining for CK7 and GATA3 was positive and therefore, pigmented mammary Paget disease was diagnosed. The patient was referred to the surgical oncology team and underwent modified radical mastectomy. No evidence of lymph node invasion was detected. At the 6-month follow up, the patient remains free of recurrence.

Teaching Point

Pigmented mammary Paget disease (PMPD) is a rare presentation of a breast intraductal carcinoma that extends to the epidermis of the nipple-areola complex [1]. The main differential diagnoses include malignant melanoma and pigmented epidermotropic metastases of breast carcinoma. PMPD dermoscopy findings include atypical pigment network, structureless blue-grey areas, brown or blue dots and globules, as well as other non-pigmented findings (structureless pink and/or white areas) [2]. Histopathology and immunohistochemistry are essential for the diagnosis. Particularly in skin of color patients, further dermoscopic descriptions are warranted, as even benign lesions (lentigo, nipple-areola melanosis, naevi, seborrheic keratosis) can resemble PMPD. Therefore, new-onset, evolving, pigmented lesions in the nipple-areola complex should be biopsied.
References


Figure 1. Pigmented mammary Paget disease. (A) Clinical inspection revealed a heterogeneously pigmented, irregular lesion affecting the left nipple, surrounded by a discrete pink plaque. (B) Dermoscopy findings included an atypical pigment network admixed with structureless pink and white areas, as well as black granules/globules towards the center of the lesion.
Eruptive Xanthoma as a Sign of Underlaying Severe Metabolic Disorder

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Keywords: eruptive xanthoma, hypertriglyceridemia, dermoscopy, xanthomatosis

Case Presentation

A 40-year-old woman presented with a 2 year history of multiple asymptomatic yellow-erythematous papules and plaques on the upper limbs, extending to the trunk and lower limbs. Dermatoscopy showed aggregates of white to yellow cloads on a structureless pink background. History of type 2 diabetes mellitus. Laboratory abnormalities occurred: triglycerides 6137 mg/dl (0-149 mg/dl), glucose 317 mg/dl (65-99 mg/dl). Histopathological examination revealed xanthomatous cells with immunohistochemistry: CD68+ in numerous histiocytes, compatible with eruptive xanthoma.

Teaching Point

Eruptive xanthomas develop in cases of pronounced and abrupt onset hypertriglyceridemia and are characterized by small, yellow, cutaneous papules, 1-4 mm in diameter, with an erythematous halo around the base. They appear suddenly in crops over pressure points and extensor surfaces of the arms, legs, and buttocks. These forms of xanthomas develop exclusively in the presence of lactescent plasma and severe hypertriglyceridemia [1].

Hypertriglyceridemia causes morbidity and mortality by significantly increasing the risk of atherosclerosis, cardiovascular disease and stroke. In addition, there is an increased risk of acute pancreatitis [2].

It is therefore very important to recognize the clinical and dermatoscopic features of the cutaneous presentation of this severe metabolic disease and request adequate laboratory workup and initiate appropriate treatment.
Figure 1. (A, B) Multiple yellow-erythematosus papules and plaques. (C) Dermatoscopy showed aggregates of white to yellow clods on a structureless pink background.

References


Longitudinal Melanonychia as the Only Sign of In Situ Squamous Cell Carcinoma

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Citation: García-Lozano JA, Salerni G, Cardenas-de la Garza JA, Perez MR, Schreiber FG. Longitudinal Melanonychia As The Only Sign Of In Situ Squamous Cell Carcinoma. Dermatol Pract Concept. 2023;13(1):e2023062. DOI: https://doi.org/10.5826/dpc.1301a62
Accepted: August 28, 2022; Published: January 2023
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Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
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Case Presentation

A 39-year-old man was consulted because of a 2-year history of a pigmented lesion in his right thumbnail (Figure 1A). His personal history was remarkable for previous genital human papillomavirus (HPV) infection. Onychoscopy revealed a pigmented longitudinal melanonychia that affected the cuticle to the distal edge of the nail plate with no other signs or symptoms (Figure 1B). Complete excision of the lesion with narrow margins was performed because of a suspicion of malignancy. Histological examination revealed in situ squamous cell carcinoma (SCC).

Teaching Point

SCC and in situ SCC are the most common malignant tumors of the nail [1]. This disease is often misdiagnosed with other common infectious or inflammatory nail diseases due to its multiple clinical presentations. Melanonychia has always been a challenging sign for dermatologists. Longitudinal melanonychia is often associated with benign or malignant melanocytic proliferation, and nail unit melanoma (NUM) should always be ruled out [2]; therefore, dermoscopy of the nail apparatus (onychoscopy) is an indispensable tool in the evaluation of pigmented nail lesions. Any unexplained melanonychia of a single digit in white-skinned individuals should be biopsied to rule out NUM; however, this case demonstrates that nail unit in situ SCC can also present exclusively as longitudinal melanonychia with no other deformity or periungual lesion and should always be included in the differential diagnosis when longitudinal melanonychia is present.
References


Figure 1. (A) Clinical image of the pigmented lesion in the right thumb nail. (B) Onychoscopy of the lesion demonstrates a brown-dark, homogeneous, pigmented, longitudinal melanonychia. Hutchison and micro-Hutchinson signs absent.
Cutaneous Lupus Erythematosus Mimicking Acne Vulgaris

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Case Presentation

A 19-year-old female presented with cicatricial acneiform lesions bilaterally on cheeks and subcutaneous nodular lesions on the bilaterally proximal aspect of the upper and lower extremities (Figure 1, A-E). She was previously diagnosed with acne vulgaris and treated with topical 2% erythromycin and isotretinoin 0.05 % gel for one year. Dermoscopic examination of the facial lesions revealed multiple linear and branching vessels over translucent yellowish-orange globular structures on scar-like areas (Figure 1, A and B). An incisional biopsy was performed from the atrophic plaque on the right arm. The histologic specimen shown lobular panniculitis accompanied by core crumbs, focal fibrin thrombi, focal hyaline necrosis, and lipomembranous changes (Figure 1G). An additional punch biopsy from the facial lesion reported a granuloma formation, perivascular and perifollicular inflammation accompanied by calcification (Figure 1H). Laboratory tests revealed positivity for double stranded DNA and antinuclear antibodies (ANA) homogeneously positive with a titer of 1:320. Anti-SS-A, anti-SS-B and anti-CCP were negative. Serum complement C3 and C4 levels were within normal limits. Based on the clinical, histopathological and laboratory findings, a diagnosis of cutaneous lupus erythematosus was made. The patient was referred to the Rheumatology department and treated with a daily regimen of azathioprine 100 mg, hydroxychloroquine 400 mg, prednisolone 5 mg and indomethacin 25 mg. Topical tacrolimus 0.03% ointment and tretinoin 0.025 % cream were also administered for the treatment of the cutaneous lesions on her face.

Teaching Point

Lupus erythematosus is one of the major imitators in dermatology and may present with various cutaneous manifestations such as symmetrical confluent erythema and edema overlying the malar cheeks, erythema and edema of the hands, symmetric erythematous eruption of non-indurated macles and papules, scaly annular lesions or papulo-squamous plaques, exfoliative erythroderma, discoid scaly purpurish macule or papules, hyperkeratotic/verrucous, bullous, urticarial or
mucosal lesions [1]. To date, acneiform presentation and granulomatous formation as seen in our patient have been rarely reported both in cutaneous and systemic lupus erythematosus [2–7] Hence, lupus erythematosus should be definitely included in the differential diagnosis of refractory acne lesions, and in these cases dermoscopy should be considered mandatory for the diagnosis of difficult-to-treat acneiform eruptions.

References


Vulvar Aphthous Ulcer in an Adolescent Girl Suffering From COVID-19 Infection

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Citation: Fotiadou C, Lazaridou E, Apalla Z. Vulvar Aphthous Ulcer in an Adolescent Girl Suffering From COVID-19 Infection. Dermatol Pract Concept. 2023;13(1):e2023054. DOI: https://doi.org/10.5826/dpc.1301a54

Accepted: July 10, 2022; Published: January 2023

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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Case Presentation

A 15-year-old girl presented with a two-day-history of a painful vulvar lesion. Clinical examination revealed a well-demarcated ulcer (2 cm) with a fibrinous center located on the left minor labia (Figure 1). There was a second smaller ulcer opposite to the large one imitating a “kissing pattern”. Both developed simultaneously. Regional lymph nodes were unaffected (no pain, no oedema). She suffered from mild systemic symptoms (low fever and rhinorrhea) and was tested positive for COVID-19 (Polymerase Chain Reaction test-PCR) three days before the appearance of the ulcer. The patient was not under treatment for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or for any other disease. Personal and family history for previous oral or vulvar aphthosis, as well as for inflammatory bowel or other autoimmune diseases, was negative. The patient had no history of prior sexual activity and serological tests for Epstein Barr, Cytomegalovirus and Syphilis were also negative. The prescribed treatment included a mid-potency topical steroid twice daily. The ulcers healed within 10 days. Both the parents and the patient gave consent to publish images of the lesion.

Teaching Point

Acute genital aphthous ulcers (AGU) or Lipschutz ulcers represent a rare, painful and distressing condition that commonly affects sexually inactive adolescent girls.[1] Although AGUs are considered an idiopathic condition, they have also been linked to several infections, autoimmune conditions and topical trauma. COVID-19, on the other hand, has been linked to several cutaneous manifestations (among which the reactivation of herpes zoster) but its relationship with AGU is still poorly clarified.[1] The most common infections, which are temporally associated with AGU, are those caused by Ebstein-Barr and Cytomegalovirus viruses and in a lesser extent by influenza and mumps viruses, as well as salmonella and mucoplasma. The underlying mechanism in these cases is probably a dysregulation of the immune system with cytokine activation due to systemic illness. The fact that Sars – Cov-2 virus causes a systemic autoimmune inflammatory response which affects multiple organ systems could be the link between the development of aphthous ulcers and COVID infection.[2]
References:


Figure 1. Aphthous ulcer located on the left labia minora of a 15-year-old girl suffering from COVID-19. The ulcer has well-demarcated borders, erythematous background and fibrinous center.
Diving Into the Blue: A Case of Melanoma Arising in a Giant Congenital Blue Nevus During Pregnancy

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Accepted: August 23, 2022; Published: January 2023
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Funding: None.
Competing Interests: None.
Authorship: All authors have contributed significantly to this publication.
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Case Presentation

Melanoma is the most frequent malignancy in pregnancy, accounting for 31% of malignant tumors diagnosed during gestation [1].

We report a case of a 28-year-old woman, pregnant at the 34th week of gestation, who had periodical skin check examination for the presence of a congenital blue nevus involving the neck, the scalp and the preauricular region (Figure 1A). During pregnancy, she self-reported the development of a solid subcutaneous 4.2 cm firm mass on her right latero-cervical region (inset).

Histological examination was consistent with melanoma developed on a congenital melanocytic blue nevus (Figure 1B). The marked melanocytic atypia and the high mitotic count allowed the differential diagnosis with a proliferative nodule in congenital nevi. At the molecular analysis, the melanoma showed no alterations in BRAF, c-Kit and all RAS. GNAQ and GNA11 mutation state was not evaluated since it is not part of our standard of care panel.

After the induction of delivery at the 38th week of gestation, histological examination of the placenta ruled out possible secondarism to the fetus.

A total body CT scan of the patient identified four solid lesions in the liver, histologically confirmed as metastasis. Final diagnosis of stage IV melanoma was made.

After a multidisciplinary discussion of the case, immunotherapy with nivolumab was started at a dosage of 240 mg iv every two weeks.

After one year of systemic treatment, the patient achieved a complete response and since the response is still maintained after four years follow up, immunotherapy has now been discontinued.
Teaching Point

European guidelines for the management of melanoma during pregnancy are still lacking, hence it is extremely challenging to decide the correct diagnostic and therapeutic approach to adopt. A multidisciplinary management is warranted and each case must be discussed on an individual patient-tailored basis [2].

References


Figure 1. (A) Clinical picture of a giant congenital blue nevus, involving the right latero-cervical region and extending to preauricular skin and to the scalp; (inset) clinical picture showing a firm solid mass, developed during pregnancy on the right latero-cervical region on congenital blue nevus. (B) Skin and soft tissue biopsy specimen showing intensely pigmented fusiform proliferation of melanocytes with mitotic figures and necrosis, finding consistent with melanoma.