Prevalence and clinical-pathological features of nevus-associated versus de novo melanoma: a retrospective cross-sectional study of 2806 cases

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Key words: melanoma, nevus-associated melanoma, de novo melanoma

DOI: https://doi.org/10.5826/dpc.1202a94

Accepted: October 19, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Nevus-associated melanoma (NAM) accounts for almost one third of all cutaneous melanomas; it is often associated with younger age, trunk location and lower Breslow’s thickness compared to de novo melanoma (DNM).

Objectives: To define the prevalence of NAM in a tertiary referral Center in Italy and to analyze its distribution according to demographics, clinical and histopathological variables

Methods: Data were retrospectively retrieved from the archive of the Pathology Unit from June 2011 to August 2020. NAMs were compared with DNM according to demographic, clinical and histopathological variables.

Results: A total of 2806 consecutive cases of melanoma were excised in 2537 patients. Of these, 431 (15.4%) were NAM. NAM patients were significantly younger than DNM patients (55.1±14.1 vs. 62.0±15.0 years, p<0.001); they were predominantly located on the trunk (64.0% vs. 47.9% of DNM). Melanoma located on the head and neck, trunk and upper limbs respectively had 2.3 (95% CI: 1.2-4.5, p<0.014), 3.2 (95% CI: 2.1-5.1, p<0.001) and 3.5 (95% CI: 2.0-6.1, p<0.001) more odds to be NAM than those on the lower limbs.
Introduction

Nevus-associated melanoma (NAM) accounts for almost one third of all cutaneous melanomas [1]. A growing body of literature demonstrated that NAM is associated with younger age, trunk location and lower Breslow’s thickness compared to de novo melanoma (DNM) [2-9].

Objectives

In this retrospective cross-sectional study, we reviewed our 10-year real-life experience at a tertiary referral center for skin cancers with the aim to analyze the prevalence of NAM and its distribution according to demographics, clinical and histopathological variables.

Methods

From the archive of the Pathology Unit, we retrieved 2806 consecutive cases of skin melanoma excised in 2537 patients from June 2011 to August 2020: 431 (15.4%) melanomas were NAM. NAMs were compared with DNMs according to demographic, clinical and histopathological variables using the Student’s T and chi square tests; statistical significance was set at p<0.05 and age was categorized according to quartiles. Statistical analysis was performed using the IBM SPSS 27.0 package (Statistical Package for Social Sciences, IBM SPSS Inc., Chicago, Ill.). The study was approved by Local Ethical Committee (protocol number: 1249/CE).

Results

Our study revealed that NAM patients were significantly younger than DNM patients (55.1 ± 14.1[standard deviation, SD] versus 62.0 ± 15.0 SD years, P < 0.001), with 67.7% NAMs having ≤61 years and 52.5% of DNMs being older than 61 years. Moreover, the NAM ratio decreased with increasing age. Interestingly, when considering body site distribution, a significant higher proportion of NAMs were on the trunk (64.0% vs. 47.9% of DNMs, NAM ratio: 19.5%) whereas DNMs were predominantly located on the lower limbs (23.9% vs. 14.7% of NAM, NAM ratio: 8.1%) (Figure 1).

No significant differences were found according to sex and Breslow’s thickness, while ulceration was significantly more observed among DNMs (Table 1).

Conclusions: Our results confirm the association of NAM with younger age and trunk location. We also demonstrated that body site differences of NAM distribution are enhanced before the sixth decade of life.

Figure 1. Ratio of nevus-associated versus de-novo melanoma according to body site and age-groups. DNM = de novo melanoma; NAM = nevus-associated melanoma.
Table 1. Demographic, clinical and histopathological features of nevus-associated vs. de-novo melanoma (NAM vs. DNM).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nevus-association</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAM ratio (%)</td>
<td>DNM ratio (%)</td>
<td>Total (count)</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Age at excision (y)</td>
<td>≤50</td>
<td>176 (40.8%)</td>
<td>576 (24.3%)</td>
<td>23.4%</td>
<td>752 (26.8%)</td>
</tr>
<tr>
<td></td>
<td>51 - 61</td>
<td>116 (26.9%)</td>
<td>551 (23.2%)</td>
<td>17.4%</td>
<td>667 (23.8%)</td>
</tr>
<tr>
<td></td>
<td>62 - 73</td>
<td>88 (20.4%)</td>
<td>651 (27.4%)</td>
<td>11.9%</td>
<td>739 (26.3%)</td>
</tr>
<tr>
<td></td>
<td>≥74</td>
<td>51 (11.8%)</td>
<td>597 (25.1%)</td>
<td>7.9%</td>
<td>648 (23.1%)</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>237 (55.0%)</td>
<td>1269 (53.4%)</td>
<td>15.7%</td>
<td>1506 (53.7%)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>194 (45.0%)</td>
<td>1106 (46.6%)</td>
<td>14.9%</td>
<td>1300 (46.3%)</td>
</tr>
<tr>
<td>Location</td>
<td>HN</td>
<td>39 (9.0%)</td>
<td>350 (14.7%)</td>
<td>10.0%</td>
<td>389 (13.9%)</td>
</tr>
<tr>
<td></td>
<td>trunk</td>
<td>276 (64.0%)</td>
<td>1138 (47.9%)</td>
<td>19.5%</td>
<td>1414 (50.4%)</td>
</tr>
<tr>
<td></td>
<td>upper limbs</td>
<td>66 (15.3%)</td>
<td>320 (13.5%)</td>
<td>17.1%</td>
<td>386 (13.8%)</td>
</tr>
<tr>
<td></td>
<td>lower limbs</td>
<td>50 (11.6%)</td>
<td>567 (23.9%)</td>
<td>8.1%</td>
<td>617 (22.0%)</td>
</tr>
<tr>
<td>Stage</td>
<td>in situ</td>
<td>203 (47.1%)</td>
<td>1183 (49.8%)</td>
<td>14.6%</td>
<td>1386 (49.4%)</td>
</tr>
<tr>
<td></td>
<td>invasive</td>
<td>228 (52.9%)</td>
<td>1192 (50.2%)</td>
<td>16.1%</td>
<td>1420 (50.6%)</td>
</tr>
<tr>
<td>Breslow (mm)</td>
<td>≤1</td>
<td>181 (79.4%)</td>
<td>881 (73.9%)</td>
<td>17.0%</td>
<td>1062 (74.8%)</td>
</tr>
<tr>
<td></td>
<td>&gt;1 &amp; ≤2</td>
<td>27 (11.8%)</td>
<td>134 (11.2%)</td>
<td>16.8%</td>
<td>161 (11.3%)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 &amp; ≤4</td>
<td>11 (4.8%)</td>
<td>87 (7.3%)</td>
<td>11.2%</td>
<td>98 (6.9%)</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>9 (3.9%)</td>
<td>90 (7.6%)</td>
<td>9.1%</td>
<td>99 (7.0%)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>superficial</td>
<td>11 (4.8%)</td>
<td>106 (8.9%)</td>
<td>9.4%</td>
<td>117 (8.2%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>431</td>
<td>2375</td>
<td>15.4%</td>
<td>2806</td>
</tr>
</tbody>
</table>

NAM, nevus-associated melanoma; DNM, de-novo melanoma; y, years; M, male; F, female, HN, head and neck; mm, millimeters.

To identify major independent factors associated with NAM status we constructed a multivariable logistic regression model with backward variables selection including sex, location, ulceration, Breslow and age categories. We demonstrated that melanoma located on the head and neck, trunk and upper limbs, respectively had 2.3 (95% confidence interval [CI] 1.2 - 4.5, P = 0.014), 3.2 (95% CI 2.1-5.1, P <0.001) and 3.5 (95% CI 2.0-6.1, P <0.001) more odds to be NAM than those on the lower limbs. Also, melanomas in patients aged ≤61 years were more likely to be NAM than those in patients ≥74 years (≤50 years: OR: 3.3; 95% CI 2.0-5.3, p<0.001; 51-61 years: OR: 2.7; 95%CI:1.6-4.5, p<0.001).

Furthermore, we reported the prevalence of NAM and DNM according to the body site in two age groups: ≤61 years and ≥74 years (NAM ratio: 20.6% and 7.9%, respectively). We found significant differences between NAM and DNM only in the ≤61 years group, with higher prevalence of NAM on the trunk (69.2%, NAM ratio 26.1%) and DNM on the lower limbs (29.1%, NAM ratio: 9.4%) (Figure 1).

Conclusions

In conclusion, although we found a lower NAM prevalence than expected from literature data, our results confirm the association of NAM with younger age and trunk location [1]. We also demonstrated that body site differences of NAM distribution are enhanced before the sixth decade of life.

Together with previous studies, our findings further support the existence of 2 divergent pathways of melanoma development [8,10].

References

An Intention-to-Treat-Analysis of the Efficacy of Immunotherapy Using Mycobacterium W Vaccine and Purified Protein Derivative of Tuberculin for Warts With Assessment of Improvement in Quality of Life

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Key words: warts, HPV, PPD tuberculin, immuvac vaccine, Mw vaccine, intralesional immunogens.


Accepted: September 29, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Lately, immunotherapy has evolved as a safe and reliable management option for treatment of warts. Various immunogens among others in use include vaccines and antigens like purified Protein Derivative of Tuberculin (PPD) and mycobacterium w (Mw) or mycobacterium indicum prani vaccines.

Objectives: The study was aimed to assess the effectiveness and safety profile of intralesional Mw vaccine against intralesional PPD for the management of multiple warts with assessment of the improvement in quality of life (QoL) using the Dermatology Life Quality Index questionnaire.

Methods: Patients aged above 12 years with ≥2 warts were recruited for the study. These individuals were randomized into groups A and B, namely Mw vaccine (group A) and PPD Tuberculin (group B). At each visit, 0.1-0.2 ml of active antigen was infiltrated intralesionally into the largest/mother wart. The injections were repeated after every 4 weeks, for the next 12 weeks. QoL improvement was measured.

Results: This intention to treat analysis was completed by 102 patients, of which 55 were in group A and 47 in group B. The rate of complete clearance was comparable in group A (76.3%) with the one in group B (65.9%, P = 0.064). Prior to treatment initiation, the most severely impacted domain of life...
by asking them to choose a number from a simple random number table. However, since this study was done in an open-label setting, both the patients and the investigators were aware of the treatment being received. The study was approved by our institutional ethical board (ethical approval number: F/SPMC/IERB/2158). Additionally, all the study participants gave their written informed consent to be recruited in the study.

Inclusion criteria
Individuals aged 12 years or above with 2 or more warts were included in our study. Only patients with either previously untreated warts, or those who had not received treatment in the last 1 month were included.

Exclusion criteria
Immunocompromised and systemically ill patients, pregnant or lactating women, and subjects with a history of any allergy or hypersensitivity reaction to any of the components of BCG, PPD or Mw in the past were excluded from the trial.

Treatment protocol
The study participants were administered either of the 2 regimens depending upon their group. Additionally, the patients were advised against taking other alternative treatments during the study period until the end of the last follow-up visit.

Individuals in group A were given with 0.1-0.2 ml of intralesional Mw vaccine (IMMUVAC 0.6 ml - Inj., Cadila Pharmaceuticals Limited) using a 26 G needle into the base of the largest wart. Correspondingly, in group B, 0.1-0.2 mL PPD Tuberculin (TUBERSOL® S1ml inj. Sanofi, containing Five (5) tuberculin units per test dose of 0.1 mL) was injected into the largest mother wart. The therapy was repeated every four weeks either until there was complete clearance in all the warts, or until 12 weeks (total 4 sessions), whichever happened first.

Follow-up and Treatment Response
After the last session (at week 12), monthly follow-up was done for the next 3 months. The treatment response was labeled as follows: complete clearance (CC) with 100% clearance of all the warty tissue and reappearance of normal skin markings, moderate clearance (MC) with 99%-25% reduction in size or number of warts, and no clearance (NC),
with < 25% reduction in size/number. Immediate or delayed adverse events were also noted at each visit. An additionally supplementary assessment to note any signs of recurrence and delayed response was also done at 6 months after the last dose.

The primary endpoint was CC of all warts at week 8 and week 12, which also included the warts that might have developed appeared or developed recurrence during the treatment period. Secondary endpoints included CC at week 24, recurrence of warts at week 12 in the patients who had clearance at week 4, and recurrence of warts at week 24 in the patients who had clearance at week 12, and the side effect profile.

The analysis of both primary and secondary endpoints was done according to an intention-to-treat (ITT) model. Randomized patients who had received at least one treatment session and returned back for at last 1 follow-up visit were included. In cases any therapy-session/follow-up visit was missed, the analysis took the status of the last-observation-carried-forward (LOCF) in order to estimate any subsequent observation points. This ITT model presumed that if a patient with warts CC was lost to follow-up, then he did not develop any new warts or experience any recurrence. Similarly, those patients who had partial or no clearance at the last visit, did not experience clearance in warts once lost to follow-up.

**Dermatology Life Quality Index (DLQI) questionnaire**

Along with the clinical response, the treatment outcome was also measured by comparing the change in the score of the hindi validated version of the DLQI questionnaire at first session (week 0), and at the end of the last follow-up visit (week 24). The questionnaire had 10 questions, each having a maximum score of 3 (total score 30). Every question had the following possible scores: not at all or not relevant or unanswered- 0; a little - 1; a lot - 2; very much - 3. Total score interpretation was done as follows: 0-1 = no effect at all on patient’s life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = exceedingly large effect. The DLQI questionnaire was supplied to all the participants at week 0 and week 24 and the improvement in QOL was noted by comparing the scores.

These questions (Q) were further divided into 6 domains in accordance with the framework of Salah, ie symptoms and feelings accompanying the disease (Q1-Q2), impairment of daily activities (Q3-Q4), effects on leisure time (Q5-Q6), effect on work/school (Q7), interpersonal relations (Q8-Q9), and impact of treatment on QOL (Q10) [5].

**Statistical Tools**

Statistical analysis was done using the Statistical Package for the Social Sciences version 20. Paired and unpaired t-tests, Chi-square test and Z scores were calculate wherever necessary. Categorical and continuous variables were presented as absolute numbers, percentages, mean, and standard deviation (SD). A p value of ≤0.05 was considered to be statistically significant.

**Results**

This intention to treat analysis included 120 subjects randomized into 2 groups with 60 patients per group. The demographic and clinical data of both groups were comparable. While 45 patients were treatment naïve, 75 had received 1 or more treatments in the past with treatment failure or relapse. The mean duration of warts in both groups was comparable (Table 1). The study was completed by 102 patients (55 in group A and 47 in group B) (Figure 1). The overall number

### Table 1. Baseline demographic data of patients

<table>
<thead>
<tr>
<th></th>
<th>Group A (Mw vaccine) N=55</th>
<th>Group B (PPD tuberculin) N=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Distribution in Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>12-55 yrs</td>
<td>12-60 yrs</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>23.5 ± 8.4 yrs</td>
<td>26.9 ± 11.7 yrs</td>
<td></td>
</tr>
<tr>
<td><strong>Gender Distribution</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>33</td>
<td>0.91</td>
</tr>
<tr>
<td>Female</td>
<td>17</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>2.2:1</td>
<td>2.3:1</td>
<td></td>
</tr>
<tr>
<td><strong>DURATION OF WARTS (IN MONTHS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.12 ± 4.01</td>
<td>8.71 ± 5.13</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean Number of Warts ± Sd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.01 ± 6.19</td>
<td>10.77 ± 7.32</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Inference: Both the groups had comparable for baseline demographics

PPD = Purified Protein Derivative of Tuberculin ; Mw = Mycobacterium w vaccine; SD = standard deviation
of patients with CC in all warts (according to ITT) was 42 and 31, in group A and B respectively during the final assessment done on at week 24 (figure 3,4,5,6) (Table 2). Between the 2 groups, the difference in the clearance rate of all warts at week at 1st, 2nd, 3rd and 4th dose was not statistically significant (Figure 2). Similarly, while comparing the response in only injected warts, the rate of CC was 85.45% (N = 47) and 76.59% (N = 36), respectively. The mean number of injections required for CC in group A were 2.38, while in group B this value was 2.56. None of the patients experienced recurrence during the ensuing follow-up period.

During the analysis of the impact of other factors on treatment response, we discovered that the mean number of warts had a significant influence on the rate of clearance (P <0.01). Patients with CC from both groups combined had 9.13 mean number of warts. Meanwhile, those with moderate to no clearance (MC and NC) had 17.26 warts. There was also a significant difference in the mean duration of warts between patients who responded and those who didn’t respond to the therapy. The combined mean duration of warts in patients from both groups with CC was 7.21 months, and that of patients with MC/NC was 9.47 months (P = 0.02).

Assessment of secondary outcomes revealed a comparable adverse reactions profile in both groups. The side effect event profile of our patients was excellent with transient injection site pain and erythema being the most common adverse events. Other rare side effects included transient fever, injection site nodule formation and transient urticaria.

While analyzing the DLQI questionnaire, the most severely affected domains were symptoms and feelings accompanying the disease (Q1 and Q2), and the inconvenience experienced by patients while seeking treatment (Q10). The
Figure 3. (A) Multiple interdigital warts at baseline. (B) Complete resolution after 4 doses of Mw vaccine.

Figure 4. (A) Multiple myrmecia wart at baseline. (B) Complete resolution after 4 doses of Mw vaccine.

Figure 5. (A) Multiple interdigital warts at baseline (B) Complete resolution after 2 doses of PPD tuberculin.
mean DLQI score of patients in group A and B at week 0 was 8.03 ± 1.03 SD and 7.96 ± 1.53 SD, respectively, which improved to 2.14 ± 0.77 SD and 2.71 ± 1.02 SD at week 24, respectively (P <0.01).

**Discussion**

The Mw vaccine is based on a cultivable non-pathogenic mycobacterium known as the mycobacterium inducus pranii, which was developed at the All India Institute of Medical Sciences in the 1970s. After more than 36 years of being tested rigorously, the vaccine was approved for the prevention of leprosy in 2019 [6]. PPD, on the other hand, is a skin antigen used for determining an immune response to tuberculosis [7]. These immunotherapeutic agents work on the principle of eliciting a Th1 mediated immune response with the production of high levels of of IL-2, IL-5, and IFN-γ.

The role of Mw for management of warts was noted for the first time by Gupta et al in genital warts with an impressive success rate of 89% [8]. Later Meena et al observed its favorable response in multiple cutaneous warts with 83% CC rates [9]. Various authors in the past have reported the effectiveness of Mw in warts to range from 55% to 93% [10-12]. While PPD was first used by Kus et al for management of warts with a success rate of only 29% [13]. Other studies have demonstrated 46% to 96% clearance rate [14-16].

We found minimal recurrence rate in our study during the ensuing 6 months follow-up period. The rate of reduction in warts was also significant and statistically comparable between the 2 groups, however, there was a higher clearance rate in patients treated with Mw vaccine. The side effect profile was also better with Mw. Serious side effects like injection site granuloma, atypical mycobacterial infection and generalized urticarial rash were seen only in PPD group. Also, the Mw group responded faster to the given treatment than PPD group.

Interestingly, there was only a marginal difference in the response rate between injected and distant warts, reinforcing our hypothesis that both Mw vaccine and PPD tuberculin could be effective even if injected intramuscularly.

One thought-provoking observation in our study was the delayed and sustained response in warts. At least 3 patients in group A and 4 in group B who only had partial clearance after the last injection, developed CC in all their warts at the end of the follow up period. It can, therefore,
be concluded that in some cases both immunogens might impart a slowly developing but long-term immunity. So, the dermatologists must counsel their patients that they must wait for at least 3 months to let the immunotherapy work. It was our observation that there was a dramatic improvement in patients’ QoL following the completion of treatment. Fifty-three (96.3%) subjects in group A and 44 (93.6%) in group B were satisfied with their treatment. The most significant improvement was seen in the domain of ‘symptoms and feelings’. A majority of patients also reported a noteworthy improvement in their interpersonal relationships.

Limitations of our study included a short follow-up period, small sample size, no analysis of genital warts, absence of a control group, and no analysis of immunological parameters. Another major limitation included the fact that we couldn’t perform any HPV tests, and therefore, we couldn’t evaluate the response according to HPV subtypes. The extrapolated results of the patients lost at follow-up in our ITT model also posed a significant limitation.

Conclusion

We found PPD and Mw to be effective in the management of extragenital warts. Both immunogens have a good safety profile and lead to a significant improvement in patients’ QoL.

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

References

Fractional Carbon Dioxide (CO\textsubscript{2}) Laser Alone Versus Fractional CO\textsubscript{2} Laser Combined With Triamcinolone Acetonide or Trichloroacetic Acid in Keloid Treatment: A Comparative Clinical and Radiological Study

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Key words: keloid, fractional laser, TAC, TCA, doppler.

Citation: El-Azhary EA, Abd Al-Salam FM, Hafiz HSA, Maghraby HM. Fractional carbon dioxide (CO\textsubscript{2}) laser alone versus fractional CO\textsubscript{2} laser combined with triamcinolone acetonide or trichloroacetic acid in keloid treatment: a comparative clinical and radiological study. Dermatol Pract Concept. 2022;12(2):e2022072. DOI: https://doi.org/10.5826/dpc.1202a72

Accepted: October 11, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Keloids are benign fibro-proliferative scarring extending outside the initial wound. Different treatment modalities as intralesional corticosteroid injection, fractional CO\textsubscript{2} laser, and others can be used either as mono or combined therapies.

Objectives: To assess the efficacy of fractional CO\textsubscript{2} laser versus fractional CO\textsubscript{2} laser accompanied with either triamcinolone acetonide or trichloroacetic acid 20% in keloid treatment clinically and radiologically.

Methods: The current study was conducted on 45 Egyptian participants with keloid scars at different sites of the body. They were classified into 3 groups treated by fractional CO\textsubscript{2} laser only (group I), fractional CO\textsubscript{2} laser followed by triamcinolone acetonide (group II), or trichloroacetic acid application (group III), respectively. Evaluation of the keloid was done with Vancouver Scar Scale (VSS) and Color Doppler Ultrasound (CDU) before and after treatment. Four sessions 4 weeks apart were applied for the patients. They were followed-up for 8 weeks after the last session.
Inclusion Criteria
Either male or female, 18 to 55 years old, duration of keloid scar of more than 6 months.

Exclusion Criteria
Patients who received any previous treatment during the 6 months before enrollment for their keloids, pregnant or lactating women, patients with photosensitivity, patients on retinoids treatment, and facial keloids.

Treatment Protocol
All patients underwent complete history taking, general and dermatological examinations, photographs, clinical assessment by Vancouver Scar Scale (VSS), and radiological assessment by Color Doppler Ultrasound (CDU) of keloids.

Materials Used
FCL, TAC, and TCA 20%.

Study design
This comparative study included 45 Egyptian participants with keloids, they were of both sexes (21 males and 24 females), and their ages were between 20 and 55 years. We classified the 45 cases into 3 groups of 15 cases each, the first group treated by FCL alone (as shown in Figure 1), the second group treated by FCL followed immediately by TAC at a dose at a dose of 0.25 ml/cm³ for keloids < 3 cm and 0.5 ml/cm³ for keloids >3 cm (equivalent to 10 mg/cm³ of TAC [40 mg/ vial]) then occluded using transparent film dressings. Patients were instructed to remove the dressing 3 hours after the session by sterile saline-soaked gauze (as shown in Figure 2) while the third group was treated by FCL followed immediately by TCA 20% application then occluded for 3 hours as in group II (as shown in Figure 3). Topical anesthesia in the form of cream (prilocaine 2.5% and lidocaine 2.5%) was applied before the laser session under occlusion for 60 minutes and wiped off with saline. Laser parameters used were: Power = 20-25 J, Stack = 1-2, Timing = 300 ms (milliseconds) and spacing = 350 mm. Evaluation of keloid scars before and after treatment was done by VSS and CDU. The patients received 4 sessions 4 weeks apart and followed-up for 8 weeks after the last session.

Results: After treatment, there was a high statistically significant reduction in VSS among the 3 groups (P ≤ 0.001); the reduction was more in group II than in I and III. Also, a high statistically significant reduction in keloid scar thickness assessed by CDU was recorded (P ≤0.001 in group II and P ≤0.01 in group I and III).

Conclusions: Combined therapy is favorable in the treatment of keloids. Trichloroacetic acid is a promising modality in treating keloid, hence it can be tried in different combinations. CDU is a promising method of keloids pre-and post-treatment assessment.

Introduction
Keloids are formed due to abnormal response of wound healing where scar tissue has grown aggressively outside the initial wound borders [1]. Treatment of keloid scar is debatable and burdensome though combined treatment modalities give better results than single ones [2]. Triamcinolone acetoneid (TAC) acts through suppression of wound inflammatory factors and fibroblast growth by decreasing transforming growth factor-beta (TGF-b) expression while stimulating the breakdown of collagen and fibroblast apoptosis, thus reducing the density of fibroblasts [3]. Fractional CO₂ laser (FCL) creates Microthermal Zones (MTZs), which occur due to tissue vaporization in the form of rows surrounded by normal skin through which they stimulate wound healing [4]. FCL can be used as a delivery system for many drugs as corticosteroids known as laser-assisted drug delivery (LADD) [5,6]. Trichloroacetic acid (TCA) induces ultrastructural changes of epidermis and dermis. TCA improves the morphologic appearance of collagen and elastin. It acts through the deposition of new collagen and normalizes elastic tissue that was destroyed due to collagen I and III overproduction and hence can be used in keloids [7].

Objectives
To assess the efficacy of FCL versus FCL accompanied with either TAC or TCA 20% in keloid treatment. Keloid treatment progress was assessed clinically and radiologically.

Materials Used
FCL, TAC, and TCA 20%.

Study design
This comparative study included 45 Egyptian participants with keloids, they were of both sexes (21 males and 24 females), and their ages were between 20 and 55 years. We classified the 45 cases into 3 groups of 15 cases each, the first group treated by FCL alone (as shown in Figure 1), the second group treated by FCL followed immediately by TAC at a dose at a dose of 0.25 ml/cm³ for keloids < 3 cm and 0.5 ml/cm³ for keloids >3 cm (equivalent to 10 mg/cm³ of TAC [40 mg/ vial]) then occluded using transparent film dressings. Patients were instructed to remove the dressing 3 hours after the session by sterile saline-soaked gauze (as shown in Figure 2) while the third group was treated by FCL followed immediately by TCA 20% application then occluded for 3 hours as in group II (as shown in Figure 3). Topical anesthesia in the form of cream (prilocaine 2.5% and lidocaine 2.5%) was applied before the laser session under occlusion for 60 minutes and wiped off with saline. Laser parameters used were: Power = 20-25 J, Stack = 1-2, Timing = 300 ms (milliseconds) and spacing = 350 mm. Evaluation of keloid scars before and after treatment was done by VSS and CDU. The patients received 4 sessions 4 weeks apart and followed-up for 8 weeks after the last session.
Evaluation Methods
Photographs by Sony Cyber shot DSC-H10, Japan camera, VSS (pliability, pigmentation, vascularity and scar thickness or height) were used, the scores range from 0 to 14 where 14 indicates the worst scar while score of 0 indicates normal skin. Keloid scar thickness measurement by CDU using a superficial probe (10 MHz) and patient satisfaction by patient satisfaction self-assessment (score from 0 to 4; not satisfied 0%, mildly satisfied <25%, moderately satisfied 25-50%, very good satisfied 50-75% or excellent satisfied ≥75%) were evaluated. Treatment side effects stated by physicians or patients were documented.

Statistical Analysis
Collected data were revised, coded, and entered into the Statistical Package for Social Science version 23. Quantitative data were presented as median, inter-quartile range when data were non-parametric. The comparison of quantitative data and non-parametric distribution between more than 2 groups was made by using Kruskall Wallis test. The comparison of quantitative data and non-parametric distribution between two paired groups was done by using Wilcoxon Rank test. The confidence interval was set at 95%, and the margin of error accepted was set at 5%. P-value was considered significant as the following: P > 0.05: non significant, P < 0.05: significant, and P < 0.01: highly significant.

Results
Forty-five adult Egyptian cases with keloids were enrolled. They were 20 -55 years old with a mean 33.69 (± 11.02 standard deviation). Among the studied groups, 24 cases were females (53.3%), while 21 were males (46.7%). The keloids were at different sites of the body (e.g. ears, chest, and back). Causes of keloid varied from trauma, surgery, spontaneous, and ear piercing. Nine cases (20%) had multiple keloids, 31 cases (80%) had keloid over bony prominences, and 8 cases were treated previously (17.8%).

Treatment Outcomes
Clinical Assessment
A high statistically significant reduction in VSS after treatment was detected among patients of the 3 groups with P <0.001. The most significant VSS reduction was in group II

Figure 1. Female patient, 32 years old with abdominal post-surgical keloid. (A) before treatment (VSS 10), (B) after 4 sessions of fractional CO2 alone (VSS became 6), showing good improvement. VSS = Vancouver Scar Scale.

Figure 2. Male patient, 23 years old with back post-traumatic keloid. (A) before treatment (VSS 9). (B) after 4 sessions of fractional CO2 followed by TAC (VSS became 2), showing excellent improvement. TAC = Triamcinolone acetonide ; VSS = Vancouver Scar Scale.
Figure 3. Female patient, 26 years old with thigh post-traumatic keloid. (A) before treatment (VSS 8). (B) after 4 sessions of fractional CO₂ followed by TCA 20% (VSS became 4), showing good improvement but hypopigmentation occurred as a side effect. TCA= Trichloroacetic acid; VSS = Vancouver Scar Scale.

Table 1. VSS Before and After Treatment For Each Group of the Studied Cases

<table>
<thead>
<tr>
<th></th>
<th>Group I No. = 15</th>
<th>Group II No. = 15</th>
<th>Group III No. = 15</th>
<th>Test value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSS before</td>
<td>Median (IQR)</td>
<td>8 (6 – 11)</td>
<td>10 (7 – 11)</td>
<td>8 (8 – 11)</td>
<td>1.546</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>4 – 13</td>
<td>6 – 13</td>
<td>5 – 14</td>
<td></td>
</tr>
<tr>
<td>VSS after</td>
<td>Median (IQR)</td>
<td>4 (3 – 8)</td>
<td>5 (4 – 8)</td>
<td>8 (5 – 9)</td>
<td>5.551</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1 – 9</td>
<td>2 – 10</td>
<td>3 – 12</td>
<td></td>
</tr>
<tr>
<td>Differences</td>
<td>Mean ± SD</td>
<td>–3.40 ± 1.18</td>
<td>–3.73 ± 1.58</td>
<td>–1.73 ± 1.33</td>
<td>13.789</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>–5 – –2</td>
<td>–7 – –2</td>
<td>–4 – 1</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.001 (HS)</td>
<td>0.001 (HS)</td>
<td>0.002 (HS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VSS = Vancouver Scar Scale; No = number; IQR= interquartile range; NS= Non significant; S= Significant; HS= highly significant; SD= standard deviation.

Table 2. Keloid Thickness by CDU Before and After Treatment For Each Group of the Studied Cases

<table>
<thead>
<tr>
<th></th>
<th>Group I No. = 15</th>
<th>Group II No. = 15</th>
<th>Group III No. = 15</th>
<th>Test value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness before (cm²)</td>
<td>Median (IQR)</td>
<td>0.81 (0.27 – 1.35)</td>
<td>1.82 (0.8 – 6.32)</td>
<td>0.36 (0.23 – 0.73)</td>
<td>11.131</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.07 – 24.5</td>
<td>0.36 – 23.85</td>
<td>0.09 – 1.4</td>
<td></td>
</tr>
<tr>
<td>Thickness after (cm²)</td>
<td>Median (IQR)</td>
<td>0.48 (0.14 – 2.07)</td>
<td>1.12 (0.36 – 5.11)</td>
<td>0.32 (0.17 – 0.59)</td>
<td>6.162</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.06 – 8</td>
<td>0.12 – 15.6</td>
<td>0.01 – 1.04</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>Mean ± SD</td>
<td>–1.55 ± 5.22</td>
<td>–1.24 ± 2.13</td>
<td>–0.12 ± 0.15</td>
<td>11.599</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>–19.6 – 1.41</td>
<td>–8.25 – 0</td>
<td>–0.41 – 0.06</td>
<td></td>
</tr>
<tr>
<td>Willcoxon Rank test</td>
<td>–2.480</td>
<td>–3.296</td>
<td>–2.513</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.013 (S)</td>
<td>0.001 (HS)</td>
<td>0.012 (S)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CDU= Color Doppler Ultrasound; No = number; IQR= interquartile range; S= Significant; HS= highly significant; SD= standard deviation.
In the current study, the relationship between clinical response measured by VSS and patient satisfaction self-assessment score was not statistically significant.

Side Effects Evaluation Among the Studied Groups
Among all patients, 20 (44.4 %) had no side effects, while 25 (55.6 %) patients had side effects in the form of pain, itching, ulceration, hypopigmentation, and hyperpigmentation. The main side effects were increased pain and itching just after the session and subsided within a week maximum in the current study. As regards types of side effects, the results showed statistically significant difference among the 3 groups (P<0.05) whereas patients of groups I and II had suffered from mild side effects as pain and itching while group III patients had suffered from severe side effects as ulceration, hypopigmentation (shown in Figure 3), and hyperpigmentation beside beside pain and itching. Neither clinical nor radiological responses had a statistically significant association with sex, or skin phototype of the patients, cause, site, size, multiplicity, or previous treatment of the keloid. However, the clinical improvement was better at non-bony sites as mean VSS reduction was -3.36 (± 1.39) while it was -2.77 (± 1.69) at bony sites. Also, no statistically significant association was found between either clinical or radiological responses and patient self-assessment score or side effects.

Conclusions
Keloid scar occurs as a result of extracellular matrix overproduction, mainly collagen. It occurs due to cytokines and growth factors overexpression [8]. Keloid formation has many theories, where the most approved one was the imbalance between collagen synthesis and degradation together with the imbalance of fibroblasts proliferation, apoptosis, and inhibition [3,9]. Keloid pathogenesis is mainly due to abnormal healing of wounds either due to abnormal response to inflammation or prolonged proliferative phase [9]. Increased collagen synthesis is related to keloid fibroblasts stimulation through inflammatory mediators, mainly transforming growth factors beta-1 (TGF-b1), TGF-b1 isoforms are supposed to be responsible for collagen overproduction by fibroblasts in pathological scars [10].

Treatment decisions must be based on the patient’s age, location, size and depth of the lesion, and past response to treatment. Hence no specific treatment is best for all keloids [11]. Regarding the current study, the results showed a statistically significant reduction in VSS score after treatment compared to before treatment in each group with P<0.01. However, the main improvement was in pliability. According to the current study, the group I received FCL as monotherapy. Compared to combined therapy in groups II and III, group I had good but not the best results.

Behera et al reported that FCL could be used in keloids excision efficiently, in agreement with the current results [12]. Also, Azzam et al reported that keloids could be treated by FCL securely and efficiently upon the results of their study on 30 patients who received 4 FCL sessions six weeks apart [13]. Nevertheless, they recommended that FCL could give better results when used as a combined therapy. As FCL inhibits TGFβ1 release but stimulates basic fibroblast growth factor (bFGF) release and hence induces epidermal regrowth and dermis collagenesis and remodeling [12,14]. The laser gives better results when used on early scars of less than 2 years [15]. In group II, for patients who received combined therapy of FCL followed by TAC this combination resulted in a significant reduction in VSS parameters after treatment compared to groups I and III with the best satisfaction score (as shown in Figures 1,2 and 3).

Al-Janahi et al treated a 72 years old African American male suffering from aggressive keloid sited at the anterior and lateral neck, back, and upper chest that lasted for 30 years resulting in flattening of keloid and improvement of pain after 1 treatment [16]. Similar to the current study, Alegre-Sánchez et al stated that using CO2 laser in combination with TAC suspension 10 % gives excellent results for keloid and hypertrophic scars treatment [17]. Also, they declared factors affecting the results of FCL followed by TAC suspension combination as the density of FCL, depth of channels created by FCL, which depend directly on laser fluency, the vehicle used, type of preparation, and formulations. In contrast, Annabathula et al reported that FCL is not recommended to treat keloids as a single therapy [18], but they recommended a combined therapy for a synergistic effect of treatment. Also, Waibel et al reported that using FCL followed by TAC suspension application in successive three treatments caused 23 % scar reduction [19]. According to Alexander et al study, they used intralesional injection instead of suspension application, giving good results [20]. Alegre-Sánchez et al reported that TAC in the form of suspension has a greater affinity than a cream or ointment, so passes through micro-channels produced by fractional ablative lasers easier [17]. Also, the improvement of texture, thickness, dyschromia, and scar functionality was reported using topical corticosteroid rather than an intralesional drug.

LADD facilitates penetration and provides better results when both medical as drugs and physical as laser treatments are combined [17]. Another key factor in LADD is the interval between using laser and drug application. Considering MTZs closure, it lasts for 6 hours after laser application; however, the vehicle or drug absorption is most successful during the first 30 minutes, while after 24 hours, no absorption is observed, so no need for further topical applications [17].

These studies came in agreement with the current study as regard laser parameters (Power = 20-25 J), the form of
In the current study, the improvement of VSS parameters after treatment (pliability, vascularity, pigmentation, and height/thickness of keloid) was statistically significant; however, the main improvement was in the pliability component, then thickness/height, then vascularity, and the least component improved was pigmentation. In agreement with the current results, Heppt et al and Azzam et al reported more evident improvement in VSS parameters, where scar pliability was markedly improved while vascularity and dyspigmentation were less pronounced [13,22]. Since biopsies in keloids are contraindicated as they can produce an increase in size, CDU can support activity assessment and indicate the response to treatment (as shown in Figures 4, 5 and 6).

Elrefaie et al and Lobos et al advised using high-resolution ultrasonography in scar assessment to determine the suitable treatment modality as an available, quick, and affordable method [23,24]. As VSS has a high range of the thickness parameter (< 2, 2-5, and > 5mm), the scar thickness may be reduced but with no changes in VSS, while ultrasound measures the whole scar thickness not only the superficial height as in VSS. Also, CDU can assess the presence of calcifications, fistulous tracts, or muscle involvement on different body sites as ear pinna and trunk.

Regarding side effects, only 25 patients had adverse events in the form of increased pain and itching just after the session and subsided within a week maximum in group I and II, while group III had suffered from severe side effects as ulceration, hypopigmentation (as shown in Figure 3), and hyperpigmentation beside pain and itching. In agreement with the current results, Alexander et al reported increased size, pain, hyperpigmentation, and hypopigmentation [20]. Also, Alegre-Sánchez et al explained that adverse effects might appear due to laser high fluencies and densities applied [17].

Ghonaim conducted a comparative study of 80% TCA multiple puncture techniques versus botulinum toxin type A (BTX-A) in keloid treatment and denoted that TCA can normalize all types of scars by dermal structure reconstruction [21]. Keloid fibroblasts have a greater capacity to proliferate and overproduce type I collagen. TCA-treated skin expresses cytokines as interleukin-10, which is involved in type I collagen synthesis, regulation, and degradation. On treating cultured dermal fibroblasts with TCA, collagen I was downregulated, and collagenase protein was upregulated, where platelet-derived growth factor-B expression was upregulated markedly, then downregulated immediately. This transient increase of platelet-derived growth factor could be beneficial for speedy wound repair [21].

In the current study, group III was treated by FCL followed by topical application of TCA 20%. TCA is a peeling agent used for superficial and medium-depth peel according to its concentration. TCA acts through coagulative necrosis and protein precipitation of epidermal cells and collagen necrosis of papillary and reticular dermis. Patients of this group had the slightest improvement of keloids with the most severe side effects as ulceration, hypopigmentation, and hyperpigmentation compared with other groups. The combination between FCL and TCA in the treatment of keloids has not been evaluated before. Hence, we tried to evaluate it through our third group.

Regarding the current study, group III was treated by FCL followed by topical application of TCA 20%. TCA is a peeling agent used for superficial and medium-depth peel according to its concentration. TCA acts through coagulative necrosis and protein precipitation of epidermal cells and collagen necrosis of papillary and reticular dermis. Patients of this group had the slightest improvement of keloids with the most severe side effects as ulceration, hypopigmentation, and hyperpigmentation compared with other groups. The combination between FCL and TCA in the treatment of keloids has not been evaluated before. Hence, we tried to evaluate it through our third group.

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Figure 4. High resolution B mode ultrasonic imaging of a cutaneous keloid with homogenous echopattern. (A) before treatment showing that keloid thickness was: 0.146 cm while the length was: 1.28 cm. (B) after 4 sessions of fractional CO\textsubscript{2} alone showing decrease in the thickness to become 0.140 cm and in the length to become 1.19 cm, showing good improvement. On CDU application the lesion was completely avascular before and after treatment. CDU = Color Doppler Ultrasound.
In the current study, regarding the site of keloid, 31 (68.9%) patients had keloids on bony prominences as chest, forearm, arm, neck, shoulder, back, interscapular, knee, and elbow, while 14 (31.1%) patients had keloids on non-bony structures as abdomen, thigh and ear lobe. We found no statistically significant relationship between the site of keloid and the clinical or radiological response; however, the clinical improvement was more at non-bony sites as mean VSS reduction was -3.36 (+1.39) while at bony sites, it was -2.77 (+1.69). We did not notice any recurrence among studied cases compared to Behera et al, who reported a high recurrence rate during a one-year follow-up period [12]. This may be due to the short period of follow-up in our study.

Current study limitations were a small sample of patients as we listed the patients who had the full number of sessions and follow-up so, we didn’t mention patients who didn’t complete the whole number of sessions, limited laser sessions, and had a short follow-up period.

FCL alone is a potent secured treatment modality of keloid, but combined therapy gives better results. However, combined therapy of FCL and topical TAC is better than monotherapy or combination with TCA in treating keloids as TCA can result in some serious side effects as ulceration, hypopigmentation, and hyperpigmentation.

Further studies of different combinations with FCL are recommended in the treatment of keloids. Also, more studies to assess the efficacy of applying TCA in lower concentrations after FCL versus TCA as monotherapy in the treatment of keloids are needed.

TCA is needed to be tried alone in treating keloid or combined with other therapies other than a fractional laser, though TCA can be combined with fractional laser but not in the same session to lessen the side effects.

Clinical assessment of keloid scar using score scales as VSS is not always accurate. It may underestimate the activity in keloid scar, so adding radiological methods in assessment...
as CDU is of great importance to help physicians in the choice of the most appropriate modality of treatment based on each scar assessed criteria.

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Features of Skin Cancer in Black Individuals: A Single-Institution Retrospective Cohort Study

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Key words: skin cancer, skin of color, ethnic skin, dermoscopy


Accepted: October 8, 2021; Published: April 2022

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Funding: Supported in part by Memorial Sloan Kettering Cancer Center’s NIH/National Cancer Institute Cancer Center support grant P30 CA008748.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Minimal knowledge exists regarding skin cancers in Black individuals, which may adversely affect patient care.

Objectives: To describe clinical features and risk factors of skin cancers in Black individuals.

Methods: Retrospective study of Black individuals diagnosed with skin cancer between January 2000 and January 2020 at our institution.

Results: 38,589 patients were diagnosed with skin cancer, of which 165 were Black individuals. One-hundred-thirteen of these Black individuals were diagnosed with melanoma, 35 with squamous cell carcinoma (SCC), and 17 with basal cell carcinoma (BCC). Most melanomas (80.0%, n = 90) were of the acral subtype; 75% (6 of 8 cases with dermoscopic images) displayed a parallel ridge pattern (PRP). The surrounding uninvolved background skin was visible in 7 cases, all demonstrating a PRP. This disappeared adjacent to most of the melanoma lesions (n = 4, 57.1%), creating a peripheral hypopigmented “halo”. The nonmelanoma skin cancers were pigmented and had similar dermoscopic features as reported in predominantly White populations. Most SCCs (n = 5, 71.4%) had a hypopigmented “halo” and most BCCs (n = 10, 55.6%) had an accentuated reticular network adjacent to the lesions.

Conclusions: Skin cancers are pigmented in Black individuals. In both acral melanomas and SCCs, we noted a peripheral rim of hypopigmentation between the lesions and the surrounding uninvolved background skin, while BCCs had accentuation of the background pigmentation adjacent to the lesions. Most acral melanomas displayed a PRP, which was also seen in surrounding uninvolved background skin.
Introduction

Skin cancer is the most common malignancy worldwide and its incidence is expected to increase [1,2]. Although much is known about the presentation of skin cancer in fair skin individuals, there is a paucity of data regarding disease morphology and contributing risk factors among those with darker skin [2-5]. This is likely secondary to the relatively higher incidence of skin cancer in those with fair skin, as well as disparities related to systemic racism in healthcare systems.

It is essential for healthcare providers to assess skin lesions with consideration of skin types. Experience has shown that skin cancer risk factors and morphology are not the same across all skin types, but there have been few studies specifically examining Black individuals [6,7]. This void increases the risk of missed diagnoses, and simultaneously may increase morbidity through the unnecessary biopsies of benign skin lesions.

Objectives

To address these knowledge gaps, we sought to describe the clinical and dermoscopic features of skin cancers in Black patients that were seen at Memorial Sloan Kettering Cancer Center (MSKCC). Additionally, we identified skin cancer risk factors and features of early disease.

Methods

This study was approved by the Institutional Review Board at MSKCC and adhered to the Helsinki declaration. We conducted a retrospective review of Black patients with biopsy-confirmed basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or melanoma seen at MSKCC between January 1st, 2000, and January 1st, 2020. We identified patients with billing record ICD diagnostic codes for these skin cancers (n = 38,948). At our institution, race/ethnicity information is collected from all patients, and we selected those who self-identified as Black (n = 359). Racial information was missing from 344 cases and these were excluded. We screened medical records and included Black patients who received treatment for skin cancers at our institution (n = 165). We conducted a review of medical records through January 2020 and recorded demographic information, medical history, and skin cancer risk factors, including a history of cancer genetic syndromes, large congenital nevi, HPV infection, trauma, burns, and immunocompromised states. Additionally, we recorded the pathology diagnosis and anatomic location of each cancer. We excluded those who did not receive treatment at our institution (n = 194) since they did not have complete reports within our medical record system.

All lesions selected for biopsy by the dermatology service undergo clinical and dermoscopic imaging. Thus, we cross-referenced all 165 cases with our image database to conduct a subset analysis on available images. Most patients (n = 146) were referred to MSKCC after a biopsy was performed by a community-based practitioner, and therefore did not have images in our database. There were clinical and dermoscopic images of 37 lesions from 19 patients (11 melanomas from 11 patients, 8 SCCs from 3 patients, and 18 BCCs from 5 patients). We evaluated images for standard dermoscopic features [8-13]. We also evaluated the surrounding uninvolved background skin to identify dermoscopic structures or patterns present in this surrounding skin.

To analyze melanoma cases, we utilized the World Health Organization melanoma classification algorithm as a basis for subtype classification [14].

Frequencies, relative frequencies, means, standard deviations (SD), and ranges were used to describe the distribution of characteristics and dermoscopic features of skin cancers.

Results

Overall Results

Our search yielded a total of 165 Black patients diagnosed with BCC, SCC, or melanoma between January 1st, 2000 and January 1st, 2020. The average age at diagnosis was 58.9 years (SD = 3.2) and 59% (n = 96) were female. One hundred and thirteen patients (68.5%) were diagnosed with melanoma, 35 (21.2%) with SCC, and 17 (10.3%) with BCC.

Acral Lentiginous Melanomas (ALM)

The majority of melanomas were acral (80.0% of all melanoma cases, n = 90), with 83.4% (n = 75) occurring on plantar surfaces, 13.3% (n = 12) in nail units, and 3.3% (n = 3) on palmar surfaces. The average age at diagnosis was 61.7 years (SD = 13.0) and 52.2% (n = 47) were male.

Most plantar ALMs were invasive (Table 1) and half of these cases were classified as AJCC 8th edition stage IV melanoma at the time of initial biopsy. All dermoscopic images (n = 8) had structureless areas with multiple colors and most had a parallel ridge pattern (PRP) (Table 2). The surrounding uninvolved background skin was visible in 7 of these cases, all demonstrating a PRP and most also demonstrating a fibrillar pattern (Figure 1). Four of these cases (57.1%) demonstrated a peripheral hypopigmented “halo” (Figure 1). Additionally, diffuse plantar lentigines were found in 5 of these cases (71.4%).

Half of the nail unit ALMs were invasive (Table 1) and two-thirds (n = 8) were classified as AJCC 8th edition stage IV melanoma at time of initial biopsy. There were dermoscopic images of 3 nail-unit melanomas, all of which were heavily pigmented (Table 2). The melanoma-in-situ
Table 1. Melanoma Characteristics

<table>
<thead>
<tr>
<th>Melanoma subtype</th>
<th>In-situ versus Invasive</th>
<th>Depth of invasion (mm) Mean (median, range)</th>
<th>Ulceration Y/N</th>
<th>Mitotic index (mit/mm²) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) in-situ</td>
<td>n (%) invasive</td>
<td>n (%) yes</td>
<td>n (%) no</td>
</tr>
<tr>
<td>Plantar ALM (n=75)</td>
<td>27 (36.00)</td>
<td>48 (64.00)</td>
<td>5.84 (4, 0.75-55)</td>
<td>37 (49.33)</td>
</tr>
<tr>
<td>Nail-unit ALM (n=12)</td>
<td>6 (50.00)</td>
<td>6 (50.00)</td>
<td>3.15 (2.9, 1.6-5)</td>
<td>4 (33.33)</td>
</tr>
<tr>
<td>Palmar ALM (n=3)</td>
<td>1 (33.33)</td>
<td>2 (66.67)</td>
<td>5.25 (5.25, 3.5-7)</td>
<td>1 (33.33)</td>
</tr>
<tr>
<td>Other melanomas on non-acral and non-mucosal surfaces (n=19)</td>
<td>1 (5.26)</td>
<td>18 (94.74)</td>
<td>7.31 (4.5, 0.4-20)</td>
<td>3 (15.79)</td>
</tr>
</tbody>
</table>

The pathologic characteristics of the melanomas observed in our Black patient population. ALM = acral lentiginous melanoma

Table 2. Dermoscopic Features of Melanomas

<table>
<thead>
<tr>
<th>Dermoscopic Features</th>
<th>Prevalence: n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acral lentiginous melanoma cases on the soles (n=8)</em></td>
<td></td>
</tr>
<tr>
<td>Structureless areas with multiple shades of brown, blue, black, and pink colors</td>
<td>8 (100.00)</td>
</tr>
<tr>
<td>Parallel ridge pattern</td>
<td>6 (75.00)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>2 (25.00)</td>
</tr>
<tr>
<td>Atypical fibrillar pattern</td>
<td>2 (25.00)</td>
</tr>
<tr>
<td>Parallel ridge pattern of surrounding skin*</td>
<td>7 (100.00)</td>
</tr>
<tr>
<td>Fibrillar pattern of surrounding skin*</td>
<td>4 (57.14)</td>
</tr>
<tr>
<td>Peripheral hypopigmentation*</td>
<td>4 (57.14)</td>
</tr>
<tr>
<td>Diffuse plantar lentigines*</td>
<td>5 (71.43)</td>
</tr>
<tr>
<td><em>Acral lentiginous melanoma cases on the nail-unit (n=3)</em></td>
<td></td>
</tr>
<tr>
<td>Hutchinson sign (pigmentation of the nail fold)</td>
<td>3 (100.00)</td>
</tr>
<tr>
<td>Brown-to-black parallel lines on the nail plate with irregular spacing, thickness, and disruption of parallelism</td>
<td>3 (100.00)</td>
</tr>
<tr>
<td>Band involving more than 2/3 of the nail plate</td>
<td>2 (66.67)</td>
</tr>
<tr>
<td>Nail dystrophy</td>
<td>1 (33.33)</td>
</tr>
</tbody>
</table>

(n = 2) demonstrated micro-Hutchinson sign and brown to black parallel lines on the nail plate with irregular spacing, thickness, and disruption of parallelism (Figure 2). The invasive melanoma (n = 1) demonstrated Hutchinson sign, pigmentation of the entire nail plate, and nail dystrophy (Figure 2).

There were only 3 palmar ALMs, 2 of which were invasive (Table 1) and classified as AJCC 8th edition stage IV melanoma at the time of initial biopsy. There were no dermoscopic images of these ALMs.

None of these patients had a family history of melanoma or had received testing for germline mutations increasing melanoma risk.

**Melanomas, Not Otherwise Specified**

Nineteen (16.8%) melanoma cases were on non-acral cutaneous surfaces, and the average age at diagnosis was 54.7 years (SD = 18.2). Twelve (63.2%) of these patients were female. Two-thirds of these cases presented as AJCC 8th edition stage IV melanoma (Table 1).
Figure 1. Acral melanoma on the sole of the foot. The normal background skin surrounding the acral melanomas had noticeable pigmentation demonstrating a parallel ridge pattern (solid oval). There was loss of the pigmentation and dermoscopic patterns surrounding the lesion itself, generating a hypopigmented “halo” around the acral lentiginous melanoma on the plantar surface. This “halo” was seen in 57.1% (n = 5) of plantar melanoma cases and was most evident in cases with the most heavily pigmented surrounding skin.

Most cases occurred on the lower extremities (31.6%, n = 6) and back (26.3%, n = 5). The most common subtype was spindle cell and/or epithelioid (36.8%, n = 7). One patient developed a dermal primary melanoma within a giant congenital nevus and no other risk factors were identified. There were no clinical or dermoscopic images.

Other melanoma subtypes included mucosal (n = 8, 7.1%), ocular (n = 4, 3.5%), and metastatic with unknown primary lesion (n = 6, 5.3%). Mucosal melanomas were located on the anus (n = 3), nasopharynx (n = 2), vagina (n = 2), and vulva (n = 1). No clinical or dermoscopic images were available.

Squamous Cell Carcinomas

There were 29 Black individuals with 35 SCCs, and the average age at diagnosis was 56 years (SD = 16). Most cases (71.4%, n = 25) were invasive. Most SCCs were located on anogenital surfaces (n = 11), lower extremities (n = 7), or the head and neck (n = 6). Known SCC risk factors were identified in 80% of patients (n = 28), including active HIV infection (n = 11), chronic wounds (n = 4), prior radiation to the area (n = 2), psoriasis (n = 2), hidradenitis suppurativa (n = 1), and lichen simplex chronicus (n = 1). HPV testing was conducted in 8 total cases, of which 7 were positive for high-risk HPV, located on the anogenital region (n = 3) and nail unit (n = 4).

There were dermoscopic images of 8 SCCs, many of which were heavily pigmented (Table 3). In the surrounding uninvolved background skin, half had a pigmented reticular network and an associated “halo” effect (Figure 3); the other half had patchy hyperpigmentation.

Figure 2. Nail melanoma cases. (A,B) The dermoscopic images of two melanoma-in-situ cases that demonstrate micro-Hutchinson sign and brown to black parallel lines on the nail plate with irregular spacing, thickness, and disruption of parallelism. (C) The clinical image of an invasive melanoma case that demonstrates and easily visible Hutchinson sign, diffuse pigmentation of the whole nail plate, and nail dystrophy.
Dermoscopic images were available for 18 BCCs (from 5 patients), all of which were pigmented (Table 3). The surrounding uninvolved background skin was assessed in 15 cases. All cases had a pigmented reticular network, and 11 cases (73.3%) had an accentuated network adjacent to the lesion (Figure 4).

**Basal Cell Carcinomas**

There were 15 Black individuals with 17 BCCs that were diagnosed and treated at our institution and the average age at diagnosis was 54.4 years (SD = 21.6). Most lesions were located on the head and neck (n = 12). Pigmentation was noted on the pathology report of 6 cases (35.3%). Pathologic subtypes included combined nodular and infiltrative (n = 6), micronodular (n = 3), nodular (n = 3), superficial (n = 3), and combined superficial and nodular (n = 1). Two patients had Gorlin syndrome, and no other risk factors were observed.

**Conclusions**

Over a 20-year period, only a small proportion of our skin cancer patients were Black individuals; this is likely due to...
that MSKCC is a tertiary cancer center and therefore it is more likely to see advanced cases.

It is interesting to note that 90.6% (n = 102) of melanomas in our population were ALM, mucosal, or ocular subtypes, all of which have not been associated with ultraviolet radiation (UVR) exposure. Superficial spreading and lentigo maligna melanomas are most closely associated with UVR exposure; these subtypes accounted for only 2 of our cases (1.8%), suggesting that UVR likely plays little to no role in the pathogenesis of melanoma in Black individuals [20-22]. As suggested by a recent systematic review, photoprotection will likely provide minimal benefit [20].

We were unable to identify any major risk factors in Black individuals. Benign pigmented macules and mottled hyperpigmentation on acral surfaces are suggested risk factors, but approximately 50% of Black individuals have these features [23-25]. While many of our patients had diffuse pigmented macules on the plantar surfaces, it is unlikely that this is a risk factor given the high prevalence of this finding and the low prevalence of melanoma in Black individuals [23,25].

The PRP has been suggested to have high sensitivity and specificity for early ALM in Caucasian and Asian populations, but it has not been validated in individuals of other races/ethnicities [26]. While the majority of our plantar melanoma cases demonstrated the PRP, these individuals also had the PRP in surrounding uninvolved background skin. A limitation of this finding is that the clinically uninvolved skin displaying the PRP was not biopsied. Therefore, it is possible
that this PRP may represent subclinical extension of the melanomas, though we believe this is unlikely since the PRP was diffusely present in the surrounding uninvolved background skin in the majority of our cases. Additionally, the PRP has been described in benign ethnic pigmented macules [27,28]. Therefore, this knowledge adds credence that the PRP may lack discriminatory power in Black individuals; if used, it may lead to an escalation of unnecessary biopsies [29]. Future studies analyzing the PRP in Black individuals may benefit from acquiring dermoscopy images of contralateral volar surfaces. Regarding other dermoscopic features observed in our ALM cases, the presence of structureless areas with multiple colors proved most useful, but this was not helpful in differentiation of in-situ and invasive disease, since cases of all stages exhibited this feature.

A novel feature we identified was a hypopigmented “halo” surrounding 57.1% (n = 4) of the plantar melanoma lesions, all of which were melanoma in-situ cases. Further studies with larger sample sizes would be helpful in identifying whether this is a sensitive and specific feature for early diagnosis.

Early detection also remains a challenge for nail-matrix melanomas, since patients of color often have benign pigmented nail bands [30]. To better understand how to differentiate these benign from malignant lesions, we need data comparing ethnic pigmented nail bands and nail-matrix melanomas. While we await such studies, reassuring factors include the involvement of multiple nails and stability over time.

Regarding the other melanoma subtypes, no identifiable risk factors were found. One patient developed a dermal melanoma within a giant congenital nevus; dermoscopy will not be useful in the early identification of these dermal lesions.

Regarding squamous cell carcinomas (SCC), UVR exposure is the most common risk factor for the development of SCC in those with fair skin, but trauma and inflammatory processes predominate the pathogenesis in Black populations, a trend also observed in our population [1,2,31-33]. Most Black patients had SCCs on non-sun exposed areas, which is consistent with other literature reports, suggesting photoprotection will likely have little to no benefit [31,32].

SCCs in Black individuals are often superficial, discrete, hard lesions arising from an indurated, rounded, elevated base [31,32]. The dermoscopic features observed in our images were similar to those described in white individuals, but there was a higher incidence of pigmented variants [8,10,31,33]. We observed a similar “halo” pattern as was described for plantar ALMs, but a larger study is needed to validate the predictive importance of this result.

Finally, in terms of our basal cell carcinomas (BCC), The majority of BCCs (70.6%) occurred on the head and neck region, suggesting UVR may play some role in the pathogenesis [34]. The low incidence of BCC in Black individuals suggests that other factors must predispose certain individuals to be more sensitive to UVR. There is a known association between skin tone and BCC risk, of which Black individuals with lighter complexions are more likely to develop BCCs [35]. Two of our patients had Gorlin syndrome, but no other risk factors were observed.

Pigmented BCCs are quite rare overall but are the most prevalent type in Black populations [34,36]. All of our dermoscopy images were heavily pigmented, and the features were consistent with those known for pigmented BCCs. We observed reticular pigmentation in the surrounding uninvolved background skin, and 55.6% (n = 10) of cases had a hyperpigmented network adjacent to the lesion. Central hypopigmentation was seen in 33.3% (n = 6) of cases. These features are not to be confused with those of a dermatofibroma, a pigment network and central scar-like white patch [37]. It is important to note that no cases were associated with significant morbidity.

Our study is limited since it is a retrospective analysis of a single tertiary cancer center. Referral bias is likely the reason for the high proportion of advanced disease cases. It is also important to consider other socioeconomic limitations that may hinder the ability of some Black patients to seek care at MSKCC. We observed that BCCs and SCCs are pigmented and demonstrate similar dermoscopic features to those reported in predominately White populations. Our study brings into question the ability of the PRP to distinguish ALM from benign acral lesions. It has been reported that the PRP can be present in benign pigmented macules on volar surfaces, and we also observed this pattern in the surrounding uninvolved background skin, bringing into question the reliability of this feature for differentiating benign and malignant lesions in Black patients. Future research is needed to elucidate whether the rim of peripheral hypopigmentation that we observed around the ALMs can assist in the differentiation of ALMs and benign pigmented macules.

Black individuals deserve equal care, which does not necessarily mean the same care. Instead, it means that Black individuals deserve customized care based on the features that may hinder the ability of some Black patients to seek care at MSKCC. We observed that BCCs and SCCs are more sensitive to UVR. There is a known association between skin tone and BCC risk, of which Black individuals with lighter complexions are more likely to develop BCCs [35]. Two of our patients had Gorlin syndrome, but no other risk factors were observed.

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Black individuals deserve equal care, which does not necessarily mean the same care. Instead, it means that Black individuals deserve customized care based on the features most useful at discriminating benign from malignant lesions. Towards this end, a better understanding of the clinical, morphologic, and dermoscopic features of skin cancers in those with darker skin is required.

References


Apremilast Survival and Reasons for Discontinuation in Psoriasis: Five-Year Experience From a Greek Tertiary Care Centre

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Key words: psoriasis, apremilast, survival, discontinuation, Greece


Accepted: December 7, 2021; Published: January 2022

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Funding: None.

Competing interests: None.

IRB approval: Ethics committee of The Hospital of Venereal and Dermatologic Diseases of Thessaloniki, Greece.

Authorship: All authors have contributed significantly to this publication

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Introduction: Drug survival is an indirect measure of efficacy and safety and its post-marketing assessment using real-life data is invaluable.

Objectives: To investigate the survival of apremilast in a cohort of psoriasis patients treated with apremilast in a Greek hospital.

Methods: A retrospective cross-sectional study examined adult psoriasis patients receiving apremilast (March 2016 to January 2021). Primary endpoint was the cumulative survival probability at 52 weeks. Kaplan-Meier analysis was used to calculate survival probability. Cox regression analysis was performed to investigate potential risk factors for apremilast discontinuation.

Results: One hundred and two patients (29.4% females) with a mean age of 55.9 years (standard deviation 15.21) were included. Sixty-five patients (63.7%) had discontinued treatment by lock date: 19 (18.6%) due to lack of efficacy, 24 (23.5%) due to loss of efficacy, 15 (14.7%) due to adverse reactions, and 7 (6.9%) due to other reasons. Cumulative survival probability at 52 weeks was 52.1%. Median survival time for all reasons for discontinuation was 58 weeks (95% Confidence Interval 40.02, 75.98).

Conclusions: Approximately half of patients remained on apremilast after 1 year of treatment. Secondary drug failure was the most common reason for discontinuation.
Introduction

Apremilast (Otezla®, Amgen) is an orally administered PDE4 inhibitor, whose efficacy and tolerability for the treatment of moderate-to-severe plaque psoriasis was investigated in the ESTEEM phase III trials [1,2]. Psoriasis treatment with biologics and small-molecule agents is of finite duration, most often due to efficacy-related reasons [3]. The probability that psoriasis patients will stay on a biologic treatment for ≥3 years is 53%-58% [4]. Anti-drug antibodies, genomic and transcriptomic parameters as well as non-compliance could possibly explain this phenomenon [4,5]. Forty-five of 382 (11.78%) ESTEEM 2 participants, who received apremilast, discontinued treatment due to lack of efficacy by week 52 [2]. Long-term (≥156 weeks) pooled data from the two ESTEEM trials showed that 34.7% of participants receiving apremilast discontinued treatment due to lack of efficacy, which was the most common reason for treatment cessation [6]. Drug survival – time from initiation to discontinuation of treatment – can be used as a surrogate measure for drug efficacy and tolerability [4]. As everyday practice may differ from the setting of clinical trials, real-world data is invaluable.

Objectives

This study was conducted to investigate the survival of apremilast in a cohort of patients treated for psoriasis in a real clinical setting.

Methods

A retrospective cross-sectional study was performed. Data was retrieved from the psoriasis archives of the 1st Dermatology Department, Aristotle University, Thessaloniki, Greece. All adult patients with any type of psoriasis, who had received at least one dose of apremilast from March 2016 until January 2021, were eligible for inclusion in the study. Dosing followed summary of product characteristics. Primary endpoint was cumulative survival probability at 52 weeks. Secondary endpoints were cumulative survival probability at weeks 24, 104, 156, and 208, percentage of patients achieving 75% reduction in their baseline Psoriasis Area Severity Index (PASI) score (PASI75) at weeks 16, 24, 52, 104 and 156 as well as mean/median drug survival for all reasons for discontinuation and stratified for specific reason (lack of and loss of efficacy, adverse events, other). Gender, age, body mass index (BMI, kg/m²), presence of scalp and nail psoriasis, presence of psoriatic arthritis, diabetes, hyperlipidaemia, hypertension and cardiovascular disease, as well as previous treatment with biologics were tested as potential predictors for drug discontinuation.

Treatment was considered discontinued if patients stopped receiving apremilast tablets. Reasons for discontinuation were primary drug failure (no ≥50% improvement in baseline PASI – PASI50 – by week 24), secondary drug failure (loss of achieved efficacy at two consecutive visits), adverse events and personal/other reasons. Patients lost to follow-up were considered to have discontinued treatment. Sequential recruitment of all eligible treated patients was performed to limit selection bias. The study protocol adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the First Dermatology Department, Aristotle University, Thessaloniki, Greece. Signed informed consent was obtained by all participating patients.

SPSS software version 25 (IBM Corp.) was used to perform all statistical analyses. Qualitative variables were described through relative frequencies. We used Shapiro-Wilk test to check for normal distribution of quantitative variables. Mean, standard deviation (SD) and 95% confidence interval (CI) were used in case of normal distribution, whereas median and interquartile range were used in the opposite case. A two-tailed significance level of <0.05 was set. Kaplan-Meier analysis was used to calculate survival probability. Study event was drug discontinuation due to any reason or loss to follow-up. Patients still on treatment were censored at the last available follow-up visit. Univariate and multivariate Cox regression analysis were performed to investigate potential risk factors for apremilast discontinuation (hazard ratio, significance level set at P ≤0.05). Akaike information criterion was used to choose the best-fitting model for survival prediction.

Results

Out of 2313 psoriasis patients registered in the psoriasis archives, 110 patients were potentially eligible for inclusion. Six
patients did not give consent for study participation and 2 patients were excluded due to incompletely recorded data. We included 102 patients in our analysis (29.4% females, 70.6% males) with various types of psoriasis and a mean age of 55.94 years (SD 15.21). Patient baseline characteristics are presented in Table 1. Patients were followed-up for a total of 26,826 patient-weeks. Sixty-five patients (63.7%) had discontinued treatment by lock date: 19 (18.6%) due to lack of efficacy, 24 (23.5%) due to loss of efficacy, 15 (14.7%) due to adverse reactions, 3 (2.94%) due to other/personal reasons, while 4 (3.92%) were lost to follow-up. Cumulative survival probability at 24, 52, 104, 156, and 208 weeks was 69.3%, 52.1%, 39.8%, 31.2%, and 28.1%, respectively (Figure 1). Mean survival time per reason for discontinuation and PASI75 achievement rates are presented in Table 1. Median survival time for all reasons for discontinuation was 58 weeks (95% CI 40.02, 75.98). The only covariate found able to predict drug survival was the combination of cardiovascular disease and diabetes, which was associated with 78% less likelihood of apremilast discontinuation (hazard ratio 0.22, P = 0.035).

<table>
<thead>
<tr>
<th>Table 1. Patient Demographic Characteristics and Apremilast Survival</th>
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<tr>
<td><strong>Sex†, n (%)</strong></td>
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<tr>
<td>Sex†, n (%):</td>
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<tr>
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<td>BMI§ (kg/m²):</td>
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<td>Due to loss of efficacy</td>
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<tr>
<td>Due to adverse events</td>
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<td>Due to other reasons (including loss to follow-up)</td>
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<td>PASI75¶</td>
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†number (percentage). ‡mean (standard deviation, 95% confidence interval). §BMI: Body Mass Index, median (interquartile range). ¶PASI75: percentage of patients having achieved 75% reduction in their baseline Psoriasis Area Severity Index score.
Figure 1. Cumulative survival probability of apremilast (Kaplan-Meier survival curve) for all reasons of drug discontinuation. Event: drug discontinuation due to any reason or loss to follow-up. Patients still on treatment were censored at the last available follow-up visit.

Conclusions

According to our results, approximately half of psoriasis patients treated with apremilast remained on treatment after one year and a little more than a quarter of them were still receiving the drug after 4 years of treatment. The most common reason for discontinuation was secondary drug failure. Patients suffering from both diabetes and cardiovascular disease were significantly less likely to discontinue apremilast. Limitations of our study are its retrospective nature, lack of a control group and absence of subgroup analysis of patients having received concurrent topical treatment.

According to real-world evidence, median apremilast survival ranges from 12.5 to 65 weeks, while 52-week survival probability ranges from 40.7% to 53.4% [7–11]. Two-year survival probability was 37.4% in a Japanese study [7]. Median time to drug discontinuation was 23 weeks for primary drug failure, 63 weeks for secondary failure and 8 weeks for adverse events [12]. Lunder et al found that apremilast had the lowest survival comparing to ustekinumab, adalimumab, etanercept, ixekizumab, infliximab and secukinumab, with ustekinumab having the longest duration in all examined psoriasis patients [3]. Patients on apremilast were more likely to discontinue treatment compared to patients on methotrexate in a nationwide French study [11]. In a cohort of patients with palmoplantar pustulosis, however, apremilast was associated with the longest survival (65 weeks) comparing to classic systemic treatments, such as cyclosporine, acitretin plus PUVA, methotrexate, acitretin, alitretinoin and fumaric acid esters [13]. Primary treatment failure was the most common reason for apremilast discontinuation in a USA study comparing various biologics and apremilast as well as in a smaller Austrian study [5,10]. Loss of efficacy was the main reason for apremilast cessation in a Japanese study (46.4%) [9]. Apremilast survival was significantly reduced in patients with scalp psoriasis (P = 0.001) in a small Spanish study [12]. The results of this study are comparable to other real-life apremilast survival data. Median apremilast survival at 52 weeks was found less than that of other systemic treatments for psoriasis, as presented in various real-life reports.

References


Clinical and Trichoscopic Graded Live Visual Scale for Androgenetic Alopecia

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Key words: androgenetic, alopecia, trichoscopy, scale


Accepted: September 15, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Currently, the mostly used classifications of androgenetic alopecia (AGA) only provide a macroscopic and subjective description of this disorder, without evaluating trichoscopic features.

Objectives: The aim of this study is to elaborate a graded live visual AGA severity scale including macroscopic and microscopic (trichoscopic) pictures, and to determine the most frequent trichoscopic characteristics associated to each grade.

Methods: A retrospective observational study was conducted on 122 patients (50 females and 72 males) affected by AGA. Macroscopic and trichoscopic photographs were taken at standardized scalp points.

Results: Each picture was ranked from AGA stage I to VII, according to Hamilton scale for men and Sinclair scale for women, and the most representative images of each severity degree were collected to produce a graded live visual scale. In males, 2 live visual scales, 1 for the anterior and 1 for posterior region of the scalp were created. In females, only 1 scale of the anterior region was realized. For each stage of severity, the corresponding trichoscopic parameters were statistically analyzed.

Conclusions: We realized new macroscopic and trichoscopic graded live visual scales for male and female patients affected by AGA, which could help physicians in giving an objective evaluation of the disease and in better managing it.
**Introduction**

Androgenetic alopecia (AGA) is one of the most common causes of hair loss in both sexes. The development and occurrence of AGA depends on multiple factors, such as genetic predisposition, endocrine and metabolic factors and exogenous causes. AGA prevalence rates in the Caucasian population are around 12% among men younger than 30 years, 50% in the fourth decade and over 90% in individuals older than 80 [1]. In women, prevalence is estimated around 16% under 50 years and 30-40% in subjects older than 70 years [2].

In male patients, hair loss typically involves temporal and vertex regions, sparing the occiput. In women, the process starts with frontal area hair thinning. Then, the parietal regions of the scalp become gradually more visible, leaving the frontal hairline intact. These different hair loss patterns are determined by differences in androgen-sensitivity of the scalp areas. Frontal and vertex regions are characterized by high expression of androgen receptors. On the contrary, occipital and temporal regions contain androgen-insensitive hair follicles [3]. Furthermore, male and female individuals show different expression of enzymes: high expression of aromatase in the anterior region of female scalp and high expression of 5α-R2 in the anterior region of male scalp.

In both sexes, AGA is characterized by progressive miniaturization of hair follicles and evolution of terminal hairs to vellus hairs. This is due to hair cycle dynamics alteration, with progressive anagen phase shortening and telogen phase prolonging [4]. Currently, the most widely used method of measuring the male AGA (MAGA) is the Hamilton–Norwood classification, developed in 1975 and characterized by stages I–VII and special types IIa–Va [5].

In 1977, Ludwig proposed a 3-grade classification for the female AGA (FAGA) [6], which is still in use today. However, in 2004, Sinclair introduced a more detailed scale, consisting of 5 pictures [7].

In 2007, Lee et al proposed a new universal classification of pattern hair loss, independent from gender: the basic and specific classification, which is based on observed patterns of hair loss, including anterior hairline shape and hair density on the frontal and vertex areas [8].

However, all the classifications formulated so far provide a descriptive, macroscopic and subjective assessment of alopecia extent and hair loss patterns.

In the last decade, several studies accumulated evidence about the use of trichoscopy in the daily clinical evaluation of hair disorders, improving the diagnostic capability beyond the simple clinical inspection [9,10]. According to this progress, a new semi-quantitative grading scale was recently proposed by Jin Nie et al. In their study, they considered some objective parameters, such as hair coverage, hair density, vellus/terminal hairs ratio, and produced a graded visual scale of six macroscopic AGA photographs [11].

**Objectives**

The aim of this study is to elaborate a graded live visual AGA severity scale including macroscopic and microscopic (trichoscopic) pictures, and to determine the most frequent trichoscopic characteristics associated to each grade.

**Methods**

We performed a single-center observational study on 122 patients (72 men and 50 women) affected by AGA. Patients were recruited in our “Skin Appendages Physiopathology Center” of Sapienza, University of Rome, from January 2019 to January 2020. AGA diagnosis was formulated through classical clinical and trichoscopic parameters, such as alopecia clinical extension and hair shaft thickness heterogeneity (anisotrichosis).

We took macroscopic photographs of each patient’s scalp using a video-dermoscope (FotoFinder®). The instrument was attached to a rotating arm of a head-positioning device (Canfield Scientific®) in order to take pictures in standardized areas of the scalp: 2 for men (frontal and vertex region) and 1 for women (only frontal region). The scalp of all subjects was combed along the midline to the sides and evaluated using the video-dermoscope. Digital trichoscopic photographs were obtained in standardized scalp areas according to patient sex: in women, photographs were collected in the scalp point corresponding to the intersection between the line connecting the ears and the line connecting the tip of the nose and the vertex (“P point”). In men, photographs were collected at the vertex (“V point”) and 2 centimeters ahead of the intersection point previously described for women (“F point”). These images were taken at 20-fold magnification, which allows high-quality enlargement of a 0.903 cm² area (field of view).

All the 122 trichoscopic pictures were analyzed with Trichoscale Pro® software, which allows to perform accurate automatic measurements of scalp structures, with subsequent manual verification. In our analysis, we considered the following trichoscopic parameters:

1. the percentage of anisotrichosis (determined as the number of not terminal hair divided by total hairs number);
2. the percentage of vellus hairs (defined as hairs with a diameter lower than 0.03 mm and shorter than 30 mm);
3. the number of empty follicles;
4. the percentage of single-hair follicular units (SHFUs);
5. the percentage of follicles with peripilar sign;
6. the presence of honeycomb pigment pattern (HCPP);
7. the presence of fibrosis.

**Acknowledgments**

None.
The first 5 parameters were selected as activity indexes, while HCPP and fibrosis were considered as marker of long-lasting disease.

Statistical Analysis

The tests used to produce the graphics of the quantitative variables were a one-way ANOVA corrected with the Sidak method and multiple t-tests, setting 95% confidence intervals. The P values of the ANOVA tests were considered statistically significant when less than 0.05. For the binomial variables we used Fisher Exact Tests with the Baptista-Pike method.

Results

Mean age was 34 (standard deviation [SD] ± 11.7) years (range: 21-83 years) for men and 52 (± 17.8 SD) years (range: 23-82 years) for women. Macroscopic pictures were then ranked by severity (7 degrees for men and 5 degrees for women), and the most representative image for each degree of severity was selected and collected, producing 3 macroscopic graded live visual scales (2 for men, 1 for women) (Figures 1, 3 and 5). Then, we selected 1 trichoscopic photograph for each grade represented on the macroscopic scale (micro and macro pictures of the same grade were taken from the same patient), producing 3 microscopic graded live visual scales (2 for men, 1 for women) (Figures 2, 4 and 6).

For each AGA and FAGA stage, the number of empty follicles, the percentage of vellus hairs, single-hair follicular units and follicles with peripilar sign were reported as graphs (Figures 7-9). We did not report data for AGA stage VII and FAGA stage V, since patients affected by very severe alopecia only showed fibrosis and HCPP. In MAGA, in both frontal and vertex areas, we observed a statistically significant increase of vellus hairs and empty follicles in relation to the clinical severity of AGA. In addition, a statistically significant increase of SHFUs correlated to the clinical stage was detected in the frontal region of MAGA patients, but not in the vertex (Figures 7, 8). In FAGA, the percentage of vellus hairs, the number of empty follicles and the number of SHFUs showed a significant increase correlated to clinical severity of alopecia (Figure 9). In all cases, the peripilar sign did not show significant variations (Figures 7-9). Prevalence of fibrosis and HCPP for each AGA and FAGA stage are reported in Table 1.

Figure 1. Graded live visual scale of male androgenetic alopecia (anterior region of the scalp): stage I, II, III, IV, V, VI and VII.

Figure 2. Corresponding trichoscopic photographs of figure 1, taken at 20-fold magnification.

Figure 3. Graded live visual scale of male androgenetic alopecia (posterior region of the scalp): stage I, II, III, IV, V, VI and VII.
and Table 2. We also evaluated the correlation between HCPP and AGA stages, finding a proportional relation between HCPP and the clinical worsening of AGA (Table 3).

The most widely used methods to classify AGA only give an idea of the extent and pattern of hair loss, without evaluating the actual severity of the disease with objective parameters. The chance to use trichoscopy in the daily clinical practice has revolutionized the approach to AGA in terms of classification and disease management. In our clinical practice, we noted that some cases of alopecia improved visibly after treatment, but their grade of classification did not vary. Moreover, some patients who were assigned the same grade of severity, according to the classic scales, presented important differences in their trichoscopic characteristics, which lead us to different therapeutic choices. In this study we wanted to underly the importance of trichoscopy in AGA classification, elaborating three macroscopic live visual scales associated to three microscopic ones. In addition, we wanted to evaluate the prevalence of trichoscopic parameters for each AGA stage and if prevalence variations between stages were statistically significant.

Hair shaft thickness heterogeneity (anisotrichosis) is an expression of the terminal hair transformation into vellus hair, suggesting that it might represent an accurate clinical sign reflecting the miniaturization process evolution, which is the basis of AGA pathogenesis [1].

Anisotrichosis higher than 20% is an essential criterion for the diagnosis of AGA [12].

Figure 4. Corresponding trichoscopic photographs of figure 3, taken at 20-fold magnification.

Figure 5. Graded live visual scale of female androgenetic alopecia (anterior region of the scalp): stage I, II, III, IV and V.

Figure 6. Corresponding trichoscopic photographs of figure 5, taken at 20-fold magnification.
Figure 7. Graphic distribution of the quantitative trichoscopic parameters according to the visual stage of male androgenetic alopecia, evaluated in a standardized area of 0.903 cm² at “F point”, accompanied by the P (* = low statistically significant, ** = mildly statistically significant, *** = highly statistically significant) of the differences observed between the various androgenetic alopecia stages.

Figure 8. Graphic distribution of the quantitative trichoscopic parameters according to the visual stage of male androgenetic alopecia, evaluated in a standardized area of 0.903 cm² at “V point”, accompanied by P (* = low statistically significant, ** = mildly statistically significant, *** = highly statistically significant) of the differences observed between the various androgenetic alopecia stages.
Indeed, all enrolled patients presented a percentage of anisotrichosis higher than 20%. In our study, male patients, at F and V points, presented a vellus hairs rate of 24% at AGA stage I and 73% at stage VI. In women, the vellus hairs rate ranged from 32% of stage I to 68% of stage IV.

**Table 1.** Presence of fibrosis at F, V and P Point, for each AGA stage (%).

<table>
<thead>
<tr>
<th>AGA</th>
<th>F point</th>
<th>V point</th>
<th>P point</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>V</td>
<td>22</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>VI</td>
<td>25</td>
<td>25</td>
<td>-</td>
</tr>
</tbody>
</table>

AGA = androgenetic alopecia.

**Table 2.** Presence of Honeycomb Pigment Pattern (HCPP) at F, V and P Point, for each androgenetic alopecia stage (%).

<table>
<thead>
<tr>
<th>AGA</th>
<th>F point</th>
<th>V point</th>
<th>P point</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>27</td>
<td>40</td>
</tr>
<tr>
<td>IV</td>
<td>63</td>
<td>62</td>
<td>100</td>
</tr>
<tr>
<td>V</td>
<td>77</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>VI</td>
<td>100</td>
<td>100</td>
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</table>

AGA = androgenetic alopecia.

**Table 3.** Odds Ratio (OR) for Honeycomb Pigment Pattern (HCPP) Associated to different AGA stages.

<table>
<thead>
<tr>
<th>HCPP</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>F point</td>
<td>67.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>V point</td>
<td>37.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>P point</td>
<td>19.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

F point: Correlation between MAGA IV-VI and MAGA I-III patients in the frontal area.

V Point: Correlation between MAGA IV-VI and MAGA I-III patients in the vertex area.

P Point: Correlation between FAGA III-IV and FAGA I-II patients.

AGA = androgenetic alopecia;
FAGA = female androgenic alopecia;
MAGA= male androgenic alopecia.

Indeed, all enrolled patients presented a percentage of anisotrichosis higher than 20%. In our study, male patients, at F and V points, presented a vellus hairs rate of 24% at AGA stage I and 73% at stage VI. In women, the vellus hairs rate ranged from 32% of stage I to 68% of stage IV.
In our study population, the increase of vellus hairs rate is related to the increase of severity stage, in both sexes. These results agree with the concept that vellus hairs rate is a trichoscopic index of disease severity.

Empty follicles have been described in AGA, especially in advanced stages of the disease [13,14]. Trichoscopically they appear as yellow dots (YD), which correspond to empty follicles filled with keratotic material and/or sebum, or follicles containing a completely miniaturized hair or a kenogen hair. If the scalp is exposed to the sun, these follicles can appear as pinpoint white dots. They occur predominantly in the frontal region, have irregular size and distribution, and are less numerous when compared to the amount found in alopecia areata. Moreover, the presence of 4 or more YD in 4 trichoscopic fields in the frontal region is one of the major trichoscopic criteria for the diagnosis of FAGA [15]. In our experience, as expected, we observed that the increase in number of empty follicles significantly correlates with AGA severity.

One follicular unit is able to produce up to 6 hairs, depending on the body region. In the human scalp, follicular units usually contain 2-4 terminal hairs and 1-2 vellus hairs. A decreased number of hairs per follicle is a characteristic feature of AGA [16, 17]. Indeed, this finding is present also in healthy individuals and patients with chronic telogen effluvium, but it is usually limited to the temporal areas.

We observed that differences in number of SHFUs between the lower stages of AGA were very little. This could be the expression of a general shortening of anagen and prolongation of telogen, which is characteristic of AGA pathogenesis, and reaches its peak in the advanced stages of this condition. Actually, in our study, the number of SHFUs correlated with AGA severity in women and in male frontal region, but not in the vertex.

Peripilar sign had been described as significantly more frequent in AGA, if compared with healthy people or patients with chronic telogen effluvium. Rakowska et al observed that the mean percentage of hair follicles with surrounding discoloration was around 32% in the frontal area and around 7% in the occipital area in patients with FAGA. Nevertheless, they documented that healthy subjects presented perifollicular discoloration in less than 25% of the follicles in the frontal area, less than 15% in the occiput and less than 20% in the temporal areas [15]. In our experience, the percentage of follicles involved by peripilar sign ranged from 13% to 43% in women, and from 9% to 37% in men. Interestingly, in our sample size, the peripilar sign did not show statistically significant variations in relation with the severity of alopecia. In fact, this trichoscopic finding corresponds to a not constant sign of inflammation and clinical activity, which may be present in both early and late stages, with no proportional correlation with the stage of AGA. Certainly, in case of peripilar sign, and consequently of inflammation, the progression of alopecia is more rapid.

Although AGA is classified within the nonscarring alopecia, the micro-inflammation involving the follicles (trichoscopically corresponding to the peripilar sign) could slowly induce the development of perifollicular fibrosis. Hence, in severe disease, it is possible for hair follicles to be replaced by connective tissue, leading to fibrous tracts, and finally causing atrophy. These empty follicles appear as white dots, which are usually observed in cicatricial alopecia, or as amorphous white cicatricial area, when the follicular ostia cannot be observed anymore [14]. In our experience, we found the highest prevalence of fibrosis in the most advanced stages of AGA reflecting a previous perifollicular inflammation and a long disease duration.

HCPP corresponds to contiguous brown rings, usually related to chronic actinic damage due to its preferentially presence in sun-exposed areas of the scalp, where hair coverage is reduced. Therefore, this do not correspond to a specific trichoscopic finding of AGA, but it is a marker of chronic and long-lasting disease, much more evident in cases of decreased hair density [18]. In our study, HCPP has been rarely observed in lower stages of AGA, with progressive increase till the 100% in the last stages. Moreover, we found a significant positive correlation between HCPP and AGA worsening. Intuitively, this result expresses the fact that, with the increase of hair thinning and hair loss, the scalp is more exposed to UV lights and cutaneous photodamage, with consequent occurrence of HCPP. Certainly, the extension of the bald area and especially the duration of the disease influence the occurrence and severity of HCPP.

Conclusions

The classification methods currently used for male and female AGA only describe the clinical pattern and the extent of disease. Therefore, they cannot be considered as objective classifications, and, frequently, do not allow to describe the real trend of hair loss because of the wide gap between different stages and since they do not take into account trichoscopic parameters.

Nowadays, trichoscopy is a fundamental tool for the management of hair loss diseases, showing high utility for their diagnosis and follow-up. Thus, trichoscopy should be considered when trying to assess a severity degree, as we performed for AGA.

Thus, we created 6 graded live visual scales, 3 macroscopic and 3 microscopic, which could help physicians in giving an objective evaluation of the disease and in better managing it.

Further studies are needed, but it is evident that only an objective trichoscopic evaluation could guide physicians to the correct management and to an appropriate “phase therapy” for AGA, as we already do for other trichological diseases.
Informed Consent: The patients in this manuscript have given written informed consent to publication of their case details.

References

Introduction: Psoriasis patients may be susceptible to malignancy due to chronic inflammation. Moreover, biological agents which are used in the treatment of psoriasis might increase the risk of malignancy due to their immunosuppressive effect.

Objectives: We evaluated the mammography results of female patients with psoriasis aged over 40 years before the initiation of biological agent treatment. We aimed to determine whether breast cancer screening with mammography should be a prerequisite before the initiation of biological agent treatment for psoriasis.

Methods: Between April 2019 and March 2021, medical records of female psoriasis patients aged over 40 years were reviewed retrospectively.

Results: This study included 42 female psoriasis patients (mean age: 53.52 ± 7.09). BI-RADS score was 2 in 18 (42.9%) patients, 1 in 13 (31%) patients, 3 in 9 (21.4%) patients and 4A in 1 (2.4%) patient. Isodense masses were detected in 10 (23.8%) patients, while 6 (14.3%) patients had intramammary lymph nodes. Mammography revealed microcalcifications in 6 (14.3%) patients, macrocalcifications in 1 (2.4%) patient and a hamartoma in 1 (2.4%) patient. Isodense masses, calcifications and intramammary lymph nodes were associated with long disease duration (> 10 years). Intramammary lymph nodes were more common in patients treated with biological agents previously compared to biologic-naive patients.

Conclusions: We suggest that female patients over 40 years, especially those who had a long disease duration, family history of breast cancer and previous history of treatment with biological agents should undergo mammography before the initiation of biological agents for the treatment of psoriasis.
Introduction
Psoriasis is a chronic inflammatory skin disorder accompanied by various comorbidities such as psoriatic arthritis, metabolic syndrome and cardiovascular disease [1]. Since chronic inflammation has been implicated in the etiopathogenesis of both psoriasis and malignancy, it has been suggested that psoriasis might be associated with increased risk of malignancy. Development of cancer was reported 1.18 times more common in patients with psoriasis compared to individuals without psoriasis [2]. Furthermore, mortality rates were elevated in accordance with the severity of psoriasis. Malignancies such as squamous cell carcinoma, lymphoma, colorectal, pancreatic, kidney, liver, esophageal and laryngeal cancer have been related to psoriasis [2]. High prevalence of breast cancer has also been reported in patients with psoriasis [3]. However, relationship between psoriasis and the risk for the development of malignancy remains controversial [4].

On the other hand, increased use of biological agents in the treatment of psoriasis leads to concerns about whether biological agents increase the risk of malignancy or not [5]. It has been suggested that tumor necrosis factor-α (TNF-α) inhibitors, anti-interleukin (IL)-12/IL-23 and anti-IL-17A antibodies might increase the risk of malignancies due to their immunosuppressive effects [6]. For instance, use of TNF-α inhibitors such as etanercept, adalimumab and infliximab longer than 12 months has been implicated in increased risk for malignancy [5]. Development of breast cancer was reported in a patient following systemic psoriasis treatment with conventional therapy, adalimumab and ustekinumab [6]. It has been suggested that breast cancer was one of the most commonly detected malignancy in patients who received ustekinumab [7]. Biological agent treatment is not recommended in patients who had an active malignancy within the last five years [8].

Evaluation of patients with psoriasis before and throughout the biological agent treatment according to their medical history of cancer and risk for the development of cancer is crucial [9]. Therefore, patients with psoriasis receiving biological agents should be encouraged to participate in national cancer screening programmes [9,10]. However, it has been reported that patients with psoriasis who were treated with biological agents did not undergo recommended tests for breast cancer screening adequately despite increased risk for malignancy [11].

Objectives
Within this study, we evaluated the mammography results of female patients with psoriasis aged over 40 years before the initiation of biological agent treatment in order to detect premalignant and malignant breast lesions. We aimed to reveal whether breast cancer screening with mammography should be a prerequisite prior to biological agent treatment for psoriasis or not.

Methods
Between April 2019 and March 2021, medical records of the female psoriasis patients aged over 40 years who underwent mammography before the initiation of biological agent treatment were reviewed retrospectively. Gazi University Ethics Committee approval was obtained for this study (approval number: 2021-412). Patients who had an increased risk for the development of breast cancer such as previous breast cancer, radiation exposure to the chest, high hereditary risk for breast cancer, patients with ovarian and endometrial malignancies and immunocompromised patients were excluded from the study. Mammography was routinely performed in female psoriasis patients over the age of 40 years before treatment with biological agents for screening premalignant or malignant lesions of the breast. Breast imaging-reporting and data system (BI-RADS) [12], breast density categories, masses, lymph nodes, calcifications and localization of the lesions were evaluated.

Statistical analysis was performed using SPSS version 20.0. Data were represented as mean ± standard deviation (SD) or median for quantitative variables, counts and percentage for categorical variables. Differences between two groups were evaluated by chi-square test. P < 0.05 was considered as statistically significant.

Results
This study included 42 female patients with a mean age of 53.52 ± 7.09 (range: 41-65 years). Thirty-two (76.2%) patients had psoriasis vulgaris, 5 (11.9%) patients had palmoplantar psoriasis and 5 (11.9%) patients had generalized pustular psoriasis (Table 1). The mean disease duration was 17.07 ± 10.99 years (range: 1-47). Twenty-eight (66.7%) patients did not complain of joint pain, whereas 14 (33.3%) patients had psoriatic arthritis. Past medical history of 16 (38.1%) patients was unremarkable. Ten (23.8%) patients had hypertension, 7 (16.7%) patients had both hypertension and type 2 diabetes, 5 (11.9%) patients had type 2 diabetes, 2 (4.8%) had hypothyroidism, 1 (2.4%) had coronary artery disease and 1 (2.4%) had granulomatous mastitis. Only 1 (2.4%) patient had a family history of breast cancer.

Forty-one (97.6%) patients were treated with conventional systemic treatments such as methotrexate, cyclosporine and acitretin, 7 (16.6%) patients were treated with phototherapy and 19 (45.2%) patients were treated with biological agents, previously. Twenty-three (54.8%) patients...
Isodense breast masses ranged between 5 to 14 mm. Furthermore, mammography revealed microcalcifications in 6 (14.3%) patients, macrocalcifications in 1 (2.4%) patient, both microcalcifications and macrocalcifications in 1 (2.4%) patient and a hamartoma in 1 (2.4%) patient.

Intramammary lymph nodes were observed in 6 (14.3%) patients, whereas mammography did not reveal an intramammary lymph node in 36 (85.7%) patients. Four (9.5%) patients had 1 intramammary lymph node, 1 (2.4%) patient had 2 and 1 (2.4%) patient had multiple intramammary lymph nodes, respectively. Intramammary lymph nodes were localized on the left breast in 4 (9.5%) patients and on the right breast in 1 (2.4%) patient. Intramammary lymph nodes were detected bilaterally in 1 (2.4%) patient. Moreover, in 1 (2.4%) patient mammography recommended further evaluation of an intramammary lymph node on the right breast, which was revealed to be reactive lymph node without an atypical cell.

The disease duration was less than 10 years in 4 (9.5%) patients with an isodense mass of the breast and more than 10 years in 6 (14.3%) patients with an isodense mass (P = 0.47). The disease duration was less than 10 years in 1 (2.4%) patient with calcifications of the breast and more than 10 years in 7 (16.7%) patients with calcifications (P = 0.21). The disease duration was less than 10 years in 1 (2.4%) patient with an intramammary lymph node and more than 10 years in 5 (11.9%) patients with intramammary lymph nodes (P = 0.41).

were biologic- naïve. Among the patients who were treated with biological agents previously, 13 (31%) patients received anti-TNF-α agents such as infliximab, adalimumab, etanercept and certolizumab pegol, 5 (11.9%) patients received both anti-TNF-α agents and ustekinumab, and 1 (2.4%) patient received ustekinumab.

Mammographic breast density was type B in 24 (57.1%) patients, type C in 13 (31%) patients, type A in 4 (9.5%) patients and type D in 1 (2.4%) patient. BI-RADS score was 2 in 18 (42.9%) patients, 1 in 13 (31%) patients, 3 in 9 (21.4%) patients and BI-RADS score was 4A in 1 (2.4%) patient. No statistically significant association was observed between BI-RADS score and disease duration or previous biological agent treatment (P = 0.51 and P = 0.65, respectively). The patient with BI-RADS 4A had microcalcifications with loose clusters in some areas, and mild pleomorphism in the upper outer quadrant of the left breast which was revealed to be nodular adenosis with columnar cell change.

Isodense masses of the breast were observed in 10 (23.8%) patients whereas mammography of 32 (76.2%) patients did not reveal a breast mass. Isodense masses were localized on the left breast in 5 (11.9%) patients and on the right breast in 2 (4.8%) patients. Moreover, in 3 (7.1%) patients, isodense masses were localized on the breasts bilaterally. Seven (16.7%) patients had 1 isodense mass, 3 (7.1%) patients had multiple isodense masses. Largest size of the isodense breast masses ranged between 5 to 14 mm. Furthermore, mammography revealed microcalcifications in 6 (14.3%) patients, macrocalcifications in 1 (2.4%) patient, both microcalcifications and macrocalcifications in 1 (2.4%) patient and a hamartoma in 1 (2.4%) patient.

Intramammary lymph nodes were observed in 6 (14.3%) patients, whereas mammography did not reveal an intramammary lymph node in 36 (85.7%) patients. Four (9.5%) patients had 1 intramammary lymph node, 1 (2.4%) patient had 2 and 1 (2.4%) patient had multiple intramammary lymph nodes, respectively. Intramammary lymph nodes were localized on the left breast in 4 (9.5%) patients and on the right breast in 1 (2.4%) patient. Intramammary lymph nodes were detected bilaterally in 1 (2.4%) patient. Moreover, in 1 (2.4%) patient mammography recommended further evaluation of an intramammary lymph node on the right breast, which was revealed to be reactive lymph node without an atypical cell.

The disease duration was less than 10 years in 4 (9.5%) patients with an isodense mass of the breast and more than 10 years in 6 (14.3%) patients with an isodense mass (P = 0.47). The disease duration was less than 10 years in 1 (2.4%) patient with calcifications of the breast and more than 10 years in 7 (16.7%) patients with calcifications (P = 0.21). The disease duration was less than 10 years in 1 (2.4%) patient with an intramammary lymph node and more than 10 years in 5 (11.9%) patients with intramammary lymph nodes (P = 0.41).
Five (11.9%) patients with an isodense mass of the breast were treated with biological agents, previously and 5 (11.9%) patients with an isodense mass were biologic-naive (P = 0.72). Three (7.1%) patients with calcifications were treated with biological agents previously, however, 5 (11.9%) patients with calcifications were biologic-naive (P = 0.62). Five (11.9%) patients with an intramammary lymph node were treated with biological agents previously and 1 (2.4%) patient with an intramammary lymph node was biologic-naive (P = 0.04).

In addition, a 58-year-old female patient with a 30-year history of psoriasis vulgaris and psoriatic arthritis who had already been diagnosed with breast cancer was determined. Family history of the patient was remarkable for both psoriasis and breast cancer. The patient was treated with methotrexate, cyclosporine, acitretin, PUVA and adalimumab, previously. After 10 months of adalimumab treatment, the patient was diagnosed with grade 1 invasive ductal carcinoma, therefore adalimumab treatment was stopped.

**Conclusions**

Breast cancer is the most frequently detected malignancy and the second most frequent reason of malignancy related mortality in women globally. Breast cancer is an insidious disease and it is usually detected by routine screening procedures [13]. However, recommendations of major guidelines for breast cancer screening in the United States differ about the initiation age of breast cancer screening with mammography, screening intervals and when to discontinue mammography [14-17].

According to the American Cancer Society, individuals without medical history of breast cancer, BRCA1/BRCA2 gene mutation and former radiation treatment to the chest at the age of 10 to 30 years are at average risk for breast cancer. The American Cancer Society recommends to start breast cancer screening with mammography for women with average breast cancer risk at 45 years of age [14]. However, women aged 40 to 44 years may also undergo mammography if they request it. The American Cancer Society recommends to repeat mammography between the ages of 45 to 54 years annually and over the age of 55 years biennially. However, women aged 55 years and over may undergo mammography annually if they request. Breast cancer screening should also proceed in healthy individuals with life expectancy longer than 10 years [14]. Nevertheless, the American College of Obstetricians and Gynecologists recommends to start mammography at the age of 40 years, however, screening may be initiated between the ages of 40 to 49 years based on shared decision of the physician and the patient. Individuals should repeat mammography every year or biennially. Mammography is not required in women older than 75 years, however, it may also be stopped in accordance with the agreement of both the physician and the patient [15]. However, US Preventive Services Task Force recommends biennial mammography screening between the ages of 50 to 74 years [16,17]. Moreover, National Comprehensive Cancer Network recommends to start mammography at the age of 40 years and to repeat it every year [15].

Breast cancer has been associated with psoriasis [18]. It has been suggested that the risk of cancer might increase in patients with psoriasis due to chronic inflammation [19]. Elevated incidence of psoriasis has also been reported among patients with breast cancer [20]. In addition, there are concerns that biological agents may be associated with cancer development based on their effect on immune system [21]. Since biological treatment has been associated with malignancy, it is mandatory to exclude malignancies before the initiation of biological agents and to monitor patients for cancer development during treatment [22].

Within this study, mammography results of patients with psoriasis over the age of 40 years were evaluated before the initiation of biological agent treatment. Most of the patients (42.9%) had BI-RADS score 2, which indicated benign findings [12]. However, BI-RADS score 3, which indicated probably benign lesions requiring close follow-up was detected in 21.4% of the patients [12]. Furthermore, 1 patient had BI-RADS score 4A, which indicated 2% to 10% of risk of malignancy [12]. Isodense masses were detected in 23.8%, microcalcifications or macrocalcifications in 19.1% and intramammary lymph nodes in 14.3% patients. Isodense masses, calcifications and intramammary lymph nodes were more common in patients with history of psoriasis longer than 10 years. However, no statistically significant difference was observed between disease duration and the frequency of isodense masses, calcifications or intramammary lymph nodes (P = 0.47, P = 0.21, P = 0.41, respectively). On the other hand, intramammary lymph nodes were more common in patients who were previously treated with biological agents compared to biologic-naive patients (P = 0.04). In addition, a patient with family history of both psoriasis and breast cancer who had already been diagnosed with breast cancer while receiving adalimumab was detected. Therefore, we suggest that female patients over 40 years, especially those who had a long disease duration, family history of breast cancer and previous history of treatment with biological agents, should undergo mammography screening before the initiation of biological agents for the treatment of psoriasis. The limitations of this study were small sample size and lack of a control group.

British Association of Dermatologists recommends the evaluation of psoriasis patients before the treatment with biological agents according to existing cancer or future malignancy risk and thus it directs patients to attend the national...
cancer screening programmes [9]. Concerning with cancer and biological agents, Joint American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guideline recommends patients to attend current and age-appropriate cancer screening [10,23]. European S3-Guideline suggests to perform clinical examination during the treatment of psoriasis with adalimumab, etanercept, infliximab and secukinumab [24,25]. Moreover, Japanese guidance for use of biologics for psoriasis recommends to collect medical history of malignancy from patients with psoriasis before the initiation of biological agent treatment [26].

Guidelines for the treatment of psoriasis with biological agents recommend to assess patients with medical history and physical examination to exclude malignancy [9,10,24-26]. However, British Association of Dermatologists guidelines for biologic therapy for psoriasis and Joint AAD-NPF point out the importance of the attendance of psoriasis patients to the national cancer screening programmes [9,10]. In the light of this information, there is no consensus on breast cancer screening guidelines regarding the necessity of clinical breast examination, initiation or cessation age of mammography and screening intervals [14-17]. Interestingly, the American Cancer Society does not recommend clinical breast examination. However, American College of Obstetricians and Gynecologists and National Comprehensive Cancer Network recommend clinical breast examination every 1 to 3 years in women aged 25-39 years and every year in women aged over 40 years [14,15]. Moreover, the American Cancer Society and American College of Obstetricians and Gynecologists stated that initiation or cessation age and screening intervals of mammography might be determined based on the preference of patients who had an average risk for breast cancer [14,15].

Since breast cancer is the most common malignancy in women, mammography should be considered as a prerequisite prior to initiation of biological agents in female patients with psoriasis. Discrepancies between breast cancer screening guidelines may lead psoriasis patients to non-adherence with cancer screening recommendations. Therefore, patients with psoriasis who undergo treatment with biological agents should be informed in detail about mammography screening intervals, which should also be included within psoriasis treatment guidelines.

References


Introduction: Eccrine porocarcinoma (EPC) is a rare subtype of non-melanoma skin cancer developing in the intraepithelial portion of eccrine sweat glands. It is branded with a highly metastatic potential and increased rate of local recurrence after treatment. EPC showcased a trend of developing on the extremities, with presentation on the face sparse.

Objectives: Aim of the study was to evaluate the frequency, clinical features, and course of this malignancy presented on the face.

Methods: A retrospective review of the skin cancers excised between January 2010 and June 2021 was conducted in the plastic surgery department of a tertiary hospital. Patients were included in the study if EPC on the face was histologically confirmed. A prospectively maintained clinic database and the pathological reports were used to collect data.

Results: 4 EPC cases on the face out of 3984 confirmed skin cancers were identified. None of the cases was suspected clinically, but the diagnosis was established following the histopathologic examination. An aggressive postoperative behavior was confirmed in 2 cases.

Conclusions: The variance in the clinical presentation and the non-specific characteristics are perplexing clinical diagnosis, with the histopathologic examination representing the current standard for confirmation. Early diagnosis and adequate surgical resection are recommended as treatment cornerstones. Clinical awareness ought to be raised and a definitive treatment protocol be established for optimized results.
Introduction

Skin cancer is the most common type of cancer encountered worldwide. However, skin malignancies originating from the sweat glands account only for 1% of these lesions [1]. Eccrine porocarcinoma (EPC) is a very rare subtype, representing only 0.005% of cutaneous tumors [2]. Most often witnessed in people aged over 60 years, it is characterized by a highly metastatic potential and increased rate of local recurrence, even after excision. EPC showcased a trend of developing on the extremities, with presentation on the face sparse [2].

Objectives

Aim of the current study was to evaluate the frequency, clinical features, and course of EPC presented on the face, shedding light on this rare malignancy.

Methods

An observational cohort study was conducted in the Plastic Surgery Department of a tertiary hospital, using a predetermined protocol, which conformed to the ethical guidelines of the 1975 Declaration of Helsinki, approved by the local ethical committee and adhered to the STROBE statement for cohort studies. All patients who underwent excision of a skin cancer in the department between January 2010 and June 2021 were identified. Patients were included in the study if EPC on the face was histologically confirmed. A prospectively maintained clinic database and the pathological reports were used to collect data. Outcomes of interest were the EPC incidence, the clinical and pathological characteristics and the postoperative course of the sample.

Results

Four cases of EPC out of 3984 confirmed skin tumors (frequency: 0.1%) were revealed. None of the cases was suspected clinically, but they were resected as non-melanoma skin tumors with 5-mm surgical margins (Figure 1) [3]. The diagnosis was established following the histopathologic examination, based on the presence of irregular dermis-infiltrating malignant cell clusters that showed an invasive architectural pattern (Figure 2). Tumor cells were demonstrating marked nuclear pleomorphism and prominent nucleoli, they were large polyhedral to cuboid with moderate to abundant eosinophilic and more rarely clear cytoplasm, as well as many mitotic figures (up to 6-7/HPF). Other observed features included squamous differentiation, without keratinization, ductal differentiation and focally desmoplasia. No tumor displayed granular cells or decapitated lumens, ruling out the possibility of apocrine differentiation. Ducts were revealed with Periodic acid–Schiff stain and immunohistochemically with CK19, CEA and EMA.

The characteristics and clinical course are depicted in Table 1. An aggressive behavior with local recurrence was revealed in 2 cases, despite the excision with clear margins in both cases and the radiotherapy course, which followed (Figure 3).

Conclusions

EPC is considered one of the rarest skin tumors a surgeon can encounter. Although it develops often on the extremities, the face in particular the auricle is considered an extremely rare location. Salih et al reviewed 453 EPC cases, with 40% of these located on the head and neck, but 7 cases only on the ear [4]. The cases we encountered concerned male patients exclusively, thus confirming the predilection of facial EPC towards the male gender [5]. Misdiagnosis of EPC due to its atypical presentation is highly probable. It could also be attributed to the diversity of total number of sweat glands on different parts of the body. However, current data annul this idea, as EPC occurrence is not correlated with the
highest concentration of sweat glands (palmoplantar region) [5]. Underreporting of this entity remains also a possibility. It is proposed that EPC emerges either de-novo or from a pre-existing benign poroma [2]. The ratio of malignant transformation was estimated around 18% [2]. Immunosuppression may be a contributing factor in EPC pathogenesis, as well as sun exposure [4]. Genetic predisposition may be also implicated, as p53 oncogene expression is witnessed in 88% of cases, while loss of retinoblastoma protein and over-expression of p16 gene, though not consistent, have been also reported [6,7]. None of these implicating factors could be associated with a predilection for EPC manifestation on specific areas.

From a clinical standpoint, EPC usually presents itself as an asymptomatic solitary nodule or mass which can progress to ulceration and cause pain [2]. The lesion is typically noticed over a long period of time (up to several years), although cases of rapid growth in a few months were also noted. Considering its rarity, EPC needs to be differentiated from a plethora of skin conditions such as seborrheic keratosis, pyogenic granuloma, amelanotic melanoma, squamous cell carcinoma and verruca vulgaris [2]. This task becomes even harder for the dermatologist, as most of the aforementioned

Table 1. Characteristics of the EPC cases identified

<table>
<thead>
<tr>
<th>Case</th>
<th>Month/Year</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Location</th>
<th>Diameter (mm)</th>
<th>Surgical Treatment</th>
<th>Adjuvant Treatment</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>5/2012</td>
<td>69</td>
<td>M</td>
<td>Cheek</td>
<td>13</td>
<td>Excision - primary repair</td>
<td>-</td>
<td>In 6 months</td>
</tr>
<tr>
<td>#2</td>
<td>11/2018</td>
<td>80</td>
<td>M</td>
<td>Lower lid</td>
<td>30</td>
<td>Excision - eye exenteration-temporalis flap</td>
<td>Radiotherapy</td>
<td>In 4 months</td>
</tr>
<tr>
<td>#3</td>
<td>12/2019</td>
<td>84</td>
<td>M</td>
<td>Temple</td>
<td>10</td>
<td>Excision -FTSG</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>#4</td>
<td>3/2021</td>
<td>61</td>
<td>M</td>
<td>Ear</td>
<td>22</td>
<td>Excision -postauricular flap</td>
<td>Radiotherapy</td>
<td>No (5 months postoperatively)</td>
</tr>
</tbody>
</table>

FTSG = full thickness skin grafting; M = Male.

Figure 2. Eccrine Porocarcinoma – Histology. (A) Diffuse infiltrative pattern. (B) Duct formation, nuclear pleomorphism and prominent nucleoli. (C) Immunohistochemical expression of CEA in ducts.

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<td>22</td>
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<td>Radiotherapy</td>
<td>No (5 months postoperatively)</td>
</tr>
</tbody>
</table>

FTSG = full thickness skin grafting; M = Male.

Figure 3. Eccrine Porocarcinoma – Locoregional metastasis of patient #2, 2 years following surgery and radiotherapy.
skin lesions are encountered predominantly in older people, while no clear clinical characteristics for EPC have been reported and thus clinical diagnosis often fails.

The clinical characteristics of EPC act as an insurmountable impediment to the clinical diagnosis and shifted focus on the histological examination. The presence of cytologic atypia with advancing margin and poromatous basoid cells displaying ductal differentiation confirmed the diagnosis [2]. Robson et al has described 3 histological variants. “Infiltrative” is characterized by ill-defined lower limits with malignant clusters infiltrating the dermis and hypodermis, “pushing” by well-defined lower dermal border, and “pagetoid” by intraepidermal clusters of tumoral cells, mimicking Paget disease [2]. Immunohistochemistry can be a significant diagnostic aid, including various stains for CEA, EMA, CK-7 and S-100 protein [8].

EPC is regarded as a very aggressive malignancy exhibiting high metastatic potential [2]. A 31% of regional or distant metastasis was revealed, with the most common sites being the regional lymph nodes (57.7%), and the lungs (12.8%) [4]. Mortality increases drastically in case of metastatic disease, with overall survival ranging between 5 and 24 months [5]. Local recurrence after excision is also high, reaching 25%, with the “infiltrative” and “pagetoid” subtypes being implicated most often [2,9]. Indeed, 2 of our 4 patients manifested local recurrence few months following tumor excision. Multi-nodularity and ulceration are among the signs of aggressiveness, while pedunculated tumors are less aggressive [4]. Lympho-vascular invasion, positive tumor margins, high mitotic count (> 14/HPF) and tumor depth (> 7 mm) have been proposed as predictors of worse clinical outcomes [2].

Currently, no established treatment guidelines exist. Wide local resection with confirmation of clear margins remains the optimal treatment option, achieving therapeutic outcome in 70%-80% of cases [5]. Belin et al proposed a surgical algorithm, based on the histological type [2,9]. In particular, all lesions should be excised with 3-mm clear margins and a further 5-mm margin must be achieved using a modified Mohs technique, should the “infiltrative” or the “pagetoid” subtypes be confirmed [9]. Having high suspicion for an aggressive skin tumor but no access to Mohs surgery, we performed an excision with a 5-mm margin. Involvement of lymph nodes requires surgical clearance, but little data exists to support routine lymph node dissection [10]. Adjuvant treatments have been administered in metastatic disease, with both chemotherapy and radiotherapy provoking mixed responses, which is also supported by our data [5].

Limitations of the study include the small sample size and its retrospective nature. However, the data covering a long period, the dedicated to skin cancer plastic surgery department of a tertiary hospital and the long-term follow-up of the patients with confirmed EPC of the face enabled the analysis of such a rare malignancy, mitigating the potential effect of the study limitations to the outcomes of interest.

Overall, EPC is very rarely encountered. Based on this cohort and the pertinent literature review, the evidence regarding the pathophysiology, surgical and adjuvant treatment is inconclusive and call for further reporting and analysis. Currently, awareness should be raised by the clinician to properly recognize EPC and treat promptly, and vigilance is needed, due to its high malignant nature and mortality rates.

**Learning points**

- Eccrine porocarcinoma (EPC) is an extremely rare subtype of non-melanoma skin cancer, mostly presenting in the extremities of the elderly population.
- Underreporting and misdiagnosis of EPC occurring on the face are distinct possibilities accounting for its rarity.
- Histologic examination confirms the diagnosis and identifies the histologic subtype, essential for guiding further treatment.
- EPC is regarded as a very aggressive malignancy exhibiting high rates of local recurrence and metastasis.
- Wide local excision remains the optimal treatment option, without a clear treatment protocol established up to date.
- Vigilance is mandatory for prompt recognition and treatment to avoid the high mortality rates reported.

**Acknowledgments**

The authors acknowledge the pathologist Dr. Aikaterini Zioga for her valuable assistance with the pathological data evaluation.

**References**


Association of Flame-Retardant Clothing With Mycosis Fungoides: A Retrospective Analysis

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Key words: mycosis fungoides, cutaneous T-cell lymphoma, flame-retardant clothing, flame-retardant chemicals, occupational-related exposure

Citation: Park KE, Ramachandran V, Tran J, Joshi TP, Garg N. Association of Flame-Retardant Clothing with Mycosis Fungoides: A Retrospective Analysis. Dermatol Pract Concept. 2022;12(2):e2022091. DOI: https://doi.org/10.5826/dpc.1202a91

Accepted: October 21, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Introduction: Mycosis fungoides (MF), the most prevalent form of cutaneous T-cell lymphoma (CTCL), has been associated with a variety of environmental and occupational exposures. Flame-retardant clothing (FRC), in contrast to flame-resistant clothing, is chemically treated and may constitute a previously unrecognized occupational hazard.

Objectives: To report an association between FRC and MF.

Methods: After encountering several young male patients whose onset of MF coincided with the occupational use of FRC and occupation as fire fighters, we did a retrospective search. Additional biopsy proven MF patients with use of FRC were identified by the EPIC electronic medical record using the search terms “CTCL, mycosis fungoides, flame, and flame-retardant.”

Results: Eight MF patients, all males, ranging in age from 31 years to 64 years (median age, 35 years) with exposure to FRC were identified. MF remission was noted in three patients who discontinued FRC use and in one patient who used a cotton undershirt barrier, while disease persistence was noted in one patient who continued to use FRC.

Conclusions: FRC appears to be associated with development of MF through chronic antigen stimulation. Use of FRC is an occupational hazard for fire fighters. Any patient whose MF coincides with use of FRC should avoid further exposure through avoidance or switching to clothing made from inherently flame-resistant fibers.
Introduction

Mycosis fungoides (MF), the most common form of cutaneous T-cell lymphoma (CTCL), is characterized initially by eczematous skin lesions containing clonal epidermotropic memory CD4+ T-cells [1]. Tan et al first suggested that MF is a disease of “chronic antigen stimulation” but the “antigen” is unknown [2]. Our finding of significant HLA-DR5 and DQ-301 associations with MF also supports the possibility of antigen restriction [3] (MF. As in other non-Hodgkin lymphomas, increased rates of MF have also been reported in association with occupational exposures to Agent Orange, aromatic hydrocarbons, and pesticides [4,5]. There have also been several reports of non-random clustering of MF, which further implicate possible environmental or occupational exposure as triggers for MF [6–8]. Moreover, we have demonstrated the presence of geographic hot spots in Texas, a finding consistent with the hypothesis that MF is triggered by particular exposures [9,10].

If occupation-related exposure is associated with increased MF risk, then it may result from chronic antigenic exposure to skin and inherent immune system-altering properties of the compounds [11]. Occupations previously reported to be associated with MF include painters, fire fighters, the military, and oil and chemical plant workers, which require specific workplace attire such as flame-retardant clothing (FRC). Unlike flame-resistant clothing which is made of inherently flame-resistant fibers, FRC is chemically treated and may be worn against the skin. While the specific chemicals used vary by manufacturers, historically these have included compounds such as brominated and chlorinated flame-retardants, as well as formaldehyde-based flame-retardants [12]. Many flame-retardant chemicals have been banned or voluntarily withdrawn from the market; however, they have been replaced with other brominated flame retardants. Previous studies have shown brominated and chlorinated flame retardants to be associated with adverse health effects, including reproductive toxicity, neurologic impairment, hormonal disturbances, and cancer [13–15]. The Epilymph study, a multicenter case-control study, demonstrated a significantly increased risk of mature B-cell lymphomas in patients exposed to brominated flame retardants [16].

Objectives

After encountering 3 young males who presented with early MF lesions in areas where their skin was chronically exposed to FRC, we performed a retrospective search. We report a case series of 8 patients who used FRC prior to developing MF and whose MF improved when FRC was no longer worn.

Methods

A retrospective chart review approved by the MD Anderson Institutional Review Board was performed by Dr. Naveen Garg at the University of Texas MD Anderson Cancer Center (MDACC) to identify and investigate MF patients with a history of exposure to FRC. All patients were seen by a CTCL expert dermatologist (Dr. Duvic) between May 1, 2009 and May 31, 2019. Inclusion criteria for this study were a patient age of 18 years or older, biopsy-proven MF confirmed by expert CTCL dermatopathologists at MDACC, and current/prior exposure to FRC. Patients with use of FRC were identified by searching the EPIC electronic medical record using the Garg Lab search method to create the study population [17]. Search terms included “CTCL, mycosis fungoides, flame, and flame-retardant.” Eight patients met the inclusion criteria. Descriptive and demographic data were collected for each patient including demographics (age and sex), stage at presentation, location of skin involvement, treatment history, response to treatment, and length of follow-up.

Results

We identified 8 patients with MF who had worn FRC (Table 1). All patients were men and ranged in age from 31 to 64 years (median, 35 years). We were unable to determine the exact brand of FRC used in 7 patients, although 1 patient (case #2) recalled having used “Bulwark” brand FRC. Three patients were diagnosed with stage IA MF, 3 with stage IB MF, 1 with stage IIB MF, and 1 with stage IIB MF (erythroderma with blood involvement). Body surface area involvement ranged from 0.25% to 97% (median, 18.95%). In 4 patients, we were able to ascertain the period of FRC use preceding lesion appearance: 2 patients (cases #2 and #8) had worn FRC for 2 years prior to development of MF; the other 2 patients had worn FRC for 3 (case #1) and 4 (case #4) years before developing MF. The sequential nature of MF onset after a median of 2.5 years of starting FRC use is suggestive of a causal link between MF and cutaneous exposure to FRC. Unfortunately, we were unable to assess the exact duration of FRC use prior to MF development in any of the remaining four patients.

Three patients (cases #1, 2 and 4) who discontinued use of FRC achieved near complete remission of MF with only minimal adjunctive treatment (natural UVB and topical triamcinolone); 1 patient witnessed partial MF resolution after discontinuing FRC and complete regression following radiation therapy. One patient (case #3), who continued to wear FRC required by his job, had complete remission of his MF by using a cotton undershirt barrier. One patient (case #3) continued to wear FRC without any barrier and has persistent disease. The remission of disease in patients who discontinued FRC, and the persistence of malignancy in the 1
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>HPI</th>
<th>Rash Location</th>
<th>Initial Stage/BSA</th>
<th>Topical Steroid</th>
<th>Other Interventions</th>
<th>Cessation of FRC</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31, M</td>
<td>3 yr history of pink to light brown patches beginning after starting work at an oil refinery where he used FRC</td>
<td>Popliteal fossa, hips, flanks, and groin</td>
<td>IB/18.95%</td>
<td>Y</td>
<td>NS</td>
<td>Y</td>
<td>6 mo</td>
</tr>
<tr>
<td>2</td>
<td>48, M</td>
<td>2 yr history of hypopigmented patches starting 2 yrs after beginning to wear Bulwark FRC</td>
<td>Arms, lower abdomen, thighs</td>
<td>IA/4.5%</td>
<td>Y</td>
<td>NB-UVB</td>
<td>Y</td>
<td>1 yr</td>
</tr>
<tr>
<td>3</td>
<td>35, M</td>
<td>Hyper- and hypopigmented patches with atrophy and telangiectasias of unknown duration recently diagnosed as MF; current FRC use</td>
<td>Axilla, hips, thighs, buttocks</td>
<td>IB/15%</td>
<td>Y</td>
<td>NS</td>
<td>N</td>
<td>1.5 yrs</td>
</tr>
<tr>
<td>4</td>
<td>31, M</td>
<td>4 yr history of erythematous scaly patch located where flame-retardant harness rubbed</td>
<td>Thigh</td>
<td>IA/0.25%</td>
<td>Y</td>
<td>UV-B</td>
<td>Y</td>
<td>2 yr</td>
</tr>
<tr>
<td>5</td>
<td>47, M</td>
<td>10 yr history of “psoriasis,” 4 yr history of exposure to flame retardant clothing; wears cotton undershirt after previous urticarial reaction to FRC</td>
<td>Sculp, arms, trunk, legs</td>
<td>IB/54%</td>
<td>Y</td>
<td>PUVA, topical nitrogen mustard</td>
<td>Cotton undershirt barrier</td>
<td>13 yrs</td>
</tr>
<tr>
<td>6</td>
<td>35, M</td>
<td>History of flame-retardant exposure since age 18 with erythematous patches diagnosed as MF at OSH; presented with unrelated rash</td>
<td>Dorsal feet</td>
<td>IA/% unknown</td>
<td>Unknown</td>
<td>PUVA</td>
<td>Unknown</td>
<td>6 mos at OSH</td>
</tr>
<tr>
<td>7</td>
<td>64, M</td>
<td>4 yr history of erythematous patches with desquamation initially on lower legs with previous exposure to FRC</td>
<td>Generalized</td>
<td>IIIB/97%</td>
<td>Y</td>
<td>ECP, Bexarotene 225 mg</td>
<td>Unknown</td>
<td>5 mo</td>
</tr>
<tr>
<td>8</td>
<td>35, M</td>
<td>10 yr history of erythematous patches, plaques, and tumors that began 2 yrs after starting job with exposure to FRC and gamma-radiation</td>
<td>Head, trunk, and extremities</td>
<td>IIB/48%</td>
<td>Y</td>
<td>TSEB; bexarotene 300 mg</td>
<td>Y</td>
<td>3 mo</td>
</tr>
</tbody>
</table>

BSA = body surface area; FRC = Flame-retardant clothing; M = male; N = no; No = number; NS = natural sunlight; ECP = Extracorporeal photopheresis; TSEB = total skin electron beam; PUVA = psoralen + ultraviolet A; NB-UVB = narrow band ultraviolet B; OSH = outside hospital; Y = yes; yr = year.
patient who continued FRC use, further implicate FRC as the trigger for MF induction.

While we are unable to exclude the possibility that other factors (eg environmental and occupational exposures independent of FRC use) could have also initiated MF in our patients, the distribution of lesions in sun shielded areas in most of our patients is also consistent with FRC use (although it should be noted that presentation of MF lesions in sun shielded areas is also common in MF not associated with FRC). Seven of the 8 patients (cases #1-5, 7-8) we report had MF lesions in skin regions that directly contacted FRC, suggesting that FRC exposure to the skin may have induced malignancy of skin resident T-cells. Notably, patient #4 reported a history of an erythematous scaly patch on the thigh at the exact location where the FRC harness rubbed, further strengthening the association between FRC and MF. Altogether, considering the temporal and spatial nature of the association between MF and FRC, we suggest that FRC could be the offending agent in the development of MF in our patients. Of note, treatment with topical steroids and UVB therapy was successful in producing remissions in early-stage IA or IB patients; MF did not recur following removal of the clothing and topical therapy.

Conclusions

Although the precise mechanism(s) through which FRC could have induced MF in our patients is unclear, we speculate that chemicals in FRC may have been absorbed in exposed skin causing mutations in T-cells or acting as antigens driving T-cell proliferation. Indeed, dermal absorption of flame retardants has been demonstrated in both in vitro and human studies [18,19]. Additionally, there have been other reports of undefined skin rashes associated with FRC which could have been undiagnosed MF [13,14,20]. Moreover, our proposed explanation of MF induction is consistent with the paradigm of MF pathogenesis first suggested by Tan et al, who first hypothesized that MF results from persistent antigen stimulation [2]. Although we did not have the means to conduct a patch test for FRC components, we note that a positive patch test would have lent further support to our hypothesis of antigen stimulation. Patch testing for evaluation of future MF patients with history of exposure to FRC may be suggested to further elucidate the mechanism of MF induction by FRC.

FRC use appears to be associated with MF and may be an unrecognized occupational hazard for firefighters or other chronically exposed individuals. Patients who develop suspicious rashes in areas of contact with FRC should have skin biopsies for diagnosis. Patients with MF coinciding with FRC use should limit further exposure through avoidance or switching to clothing made from inherently flame-resistant fibers. Newer inherently flame-resistant clothing alternatives use next-generation polymers and fibers rather than chemical flame-retardants. Additionally, unlike FRC, clothing from inherently flame-resistant fibers does not lose efficacy with repeated washes [21], and therefore represents both a safer and more economical option compared to FRC.

References

Efficacy and Safety of Ixekizumab Versus Adalimumab in Biologic-naïve Patients With Active Psoriatic Arthritis and Moderate-to-severe Psoriasis: 52-week Results From the Randomized SPIRIT-H2H Trial

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Key words: ixekizumab, adalimumab, SPIRIT-H2H, nail psoriasis, psoriasis,

Citation: Reich K, Kristensen LE, Smith SD et al. Efficacy and safety of ixekizumab versus adalimumab in biologic-naïve patients with active psoriatic arthritis and moderate-to-severe psoriasis: 52-week results from the randomized SPIRIT-H2H trial. Dermatol Pract Concept. 2022;12(2):e2022104. DOI: https://doi.org/10.5826/dpc.1202a104

Accepted: October 25, 2021; Published: April 2022

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Funding: This work was supported by Eli Lilly and Company, which contributed to study design, data collection, data analysis, data interpretation, manuscript preparation, and publication decisions.

Competing interests: K. Reich reports conflicts of interest from Abbvie, Affibody, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Forward Pharma, Janssen, Kyowa Kirin, Leo, and UCB. L.E. Kristensen reports conflicts of interest from Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Forward Pharma, Janssen, Merck, and Co., Novartis, Pfizer, and UCB. S.D. Smith has been an advisor for and/or received speaking fees and/or served as an investigator in clinical trials for Abbvie, Amgen, Biogen, Bristol Myers Squibb, Eli Lilly and Company, Janssen Cilag, Leo Pharma, Novartis, Pfizer, Sanofi Genzyme, and UCB. P. Rich has been a principal investigator for AbbVie, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Eli Lilly and Company, Merck, Novartis, Pfizer and Sandoz, Sun Pharma, and UCB; a consultant for Abbvie, Novartis and Polichem; and an advisory board participant for AbbVie, Eli Lilly and Company, Leo, Novartis, and Sandoz. C. Sapin, S. Liu Leage, R. McKenzie, C. Schuster, and E. Riedl are employees and minor shareholders of Eli Lilly and Company. M. Gooderham has received grant/research support from: AbbVie, Actelion Pharmaceuticals, Akros Pharma, Amgen, Arcutis Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Dermavant, Eli Lilly and Company, Galderma SA, Incyte, Kyowa Kirin, Janssen, LEO Pharma, Medimmune, Merck and Co., Novartis, Pfizer, Regeneron Pharmaceuticals, Roche Laboratories, Sanofi Genzyme, UCB, and Bausch/Valent Pharmaceuticals. Consultant for: Akros Pharma, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Janssen, Novartis, Sanofi Genzyme, Valeant Pharmaceuticals. Speakers bureau for: AbbVie, Amgen, Arcutis, Boehringer Ingelheim International GmbH, Celgene, Eli Lilly and Company, Galderma SA, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, and UCB.

Authorship: All authors have contributed significantly to this publication

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Introduction: The randomized, open-label, assessor-blinded, parallel-group SPIRIT-H2H trial (NCT03151551) demonstrated superiority of ixekizumab over adalimumab in simultaneously achieving improvement in joint symptoms (American College of Rheumatology [ACR]50) and skin clearance (Psoriasis Area and Severity Index [PASI]100) in biologic-naive patients with active psoriatic arthritis (PsA) and plaque psoriasis (PsO) at Week (W) 24. Higher efficacy of ixekizumab versus adalimumab was maintained through W52.

Objectives: This analysis investigated efficacy and safety of ixekizumab and adalimumab in the subgroup of patients with PsA and moderate-to-severe PsO through W52.

Methods: Efficacy and safety outcomes were analyzed in patients with PsA and moderate-to-severe PsO (PASI ≥ 12, Body Surface Area ≥ 10%, static Physician Global Assessment ≥ 3) through W52. Categorical and continuous outcomes were analyzed using logistic regression models and mixed model for repeated measures, respectively.

Results: More ixekizumab- versus adalimumab-treated patients simultaneously achieved PASI100 and ACR50 at W24 (40.8% versus 17.6%, P = 0.015) and W52 (38.8% versus 17.6%, P = 0.026). Likewise, more ixekizumab- versus adalimumab-treated patients achieved PASI100 (59.2% versus 25.5%, P = 0.001) and PASI90 (81.6% versus 60.8%, P = 0.028) through W52, and nail PsO clearance at W24. Joint symptom improvements were comparable between groups. No new safety findings were reported.

Conclusions: Ixekizumab had higher efficacy than adalimumab in simultaneous achievement of ACR50 and PASI100 at W24 and W52 in patients with PsA and moderate-to-severe PsO. Ixekizumab-treated patients showed higher response rates for nail PsO clearance and for reporting minimal or no impact on quality of life at W24.
Methods

Participants and Study Design

SPIRIT-H2H (Clinicaltrials.gov: NCT03151551) is a 52-week, multicenter, randomized, open-label, assessor-blinded, parallel-group study evaluating the efficacy and safety of IXE versus ADA in biologic-naive, csDMARD-inadequate-responder patients with active PsA and PsO. The study population and study design have been previously published [18]. Briefly, patients were aged ≥ 18 years, had a confirmed diagnosis of PsA of ≥ 6 months, had active PsA (≥ 3/66 swollen joints and ≥ 3/68 tender joints) and PsO (≥ 3% of the Body Surface Area [BSA] affected), fulfilled the Classification for Psoriatic Arthritis (CASPAR) criteria and were not previously treated with biologics or Janus kinase inhibitors. Patients on csDMARDs at screening were permitted to continue at a stable dose. Randomization was stratified by concomitant csDMARD use and moderate-to-severe PsO involvement (PASI ≥ 12, BSA ≥ 10%, and static Physician Global Assessment [sPGA] ≥ 3) at baseline.

Patients were randomized at a 1:1 ratio to receive IXE or ADA. Patients with active PsA and moderate-to-severe PsO were treated as per approved label for moderate-to-severe PsO and received a 160 mg IXE starting dose at W0, followed by 80 mg IXE every 2 weeks (Q2W) from W2 to W12 and every 4 weeks thereafter, or an 80 mg ADA starting dose, followed by 40 mg ADA Q2W starting at W1.

In this post hoc analysis, only patients with active PsA and moderate-to-severe PsO at baseline were included.

SPIRIT-H2H was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the ethical review boards of all participating sites prior to the start of study-related procedures. Informed consent was obtained from all participants.

Efficacy Endpoints

Endpoints were assessed in all patients with active PsA and moderate-to-severe PsO at baseline. The primary endpoint of SPIRIT-H2H was the proportion of patients who simultaneously achieved ACR50 and PASI100 responses at W24. Major secondary endpoints were the proportion of patients achieving ACR50 and the proportion of patients achieving PASI100 at W24.

Endpoints at W52 included the proportion of patients simultaneously achieving ACR50 and PASI100 responses, PASI100, PASI90 or PASI75 responses, change from baseline in Dermatology Life Quality Index (DLQI) total score, proportion of patients achieving DLQI (0,1), change from baseline in the Itch Numeric Rating Scale (NRS) score, proportion of patients achieving Itch NRS score = 0, and change from baseline in the Nail Psoriasis Severity Index (NAPSI) fingernails score and proportion of patients achieving complete clearance of nail psoriasis (NAPSI = 0) in the subgroup of patients with NAPSI ≥ 1 at baseline.

Safety

Treatment-emergent adverse events (TEAEs) were defined as events that initially occurred or worsened in severity after the first dose of the study treatment and on or before the date of the final visit within the treatment period. Adverse events (AEs) of special interest included infections, injection site reactions, malignancies, major adverse cardiovascular events, allergic reactions/hypersensitivity, inflammatory bowel disease, depression, hepatic laboratory changes, cytopenia, and neutropenia. Cerebrocardiovascular events were adjudicated by external clinical events committees. Safety results for the total study population have been published previously [18,19].

Statistical Analysis

Efficacy

In this post hoc analysis, efficacy analyses were performed on the intent-to-treat population, consisting of all randomized patients according to the treatment assigned at W0. Categorical variables were assessed using logistic regression models with treatment and concomitant csDMARD use at baseline as factors, as well as Fisher’s exact tests whenever relevant. The non-responder imputation (NRI) method was used in case of missing data: patients were considered non-responders if they did not meet the clinical response criteria or had missing clinical response data at a particular time point of analysis. Continuous variables were analyzed using a mixed effects model of repeated measures analysis, which included treatment group, concomitant csDMARD use at baseline, and visit as fixed factors, baseline value as a covariate, and baseline-by-visit and treatment-by-visit interaction terms.

Safety

Descriptive statistics were performed on the safety population, defined as all randomized patients who received ≥ 1 dose of the study treatment.

Results

Baseline Characteristics

Of the 566 biologic-naive patients included in the SPIRIT-H2H study, 49 (17.3%) of the IXE-treated patients and 51 (18.0%) of the ADA-treated patients had moderate-to-severe PsO (PASI ≥ 12, sPGA ≥ 3, and BSA ≥ 10%) at baseline. The frequency of moderate-to-severe PsO and PsO in the overall SPIRIT-H2H population is visually...
IXE- and ADA-treated patients, respectively, had concomitant methotrexate (MTX) use at baseline, which was permitted throughout the study.

Baseline demographics and disease characteristics were mostly balanced between the IXE and ADA groups (Table 1). Totals of 51.0% and 54.9% of IXE- and ADA-treated patients, respectively, had concomitant methotrexate (MTX) use at baseline, which was permitted throughout the study.

### Table 1. Baseline demographics and disease characteristics of patients with PsA and moderate-to-severe PsO

<table>
<thead>
<tr>
<th>Category</th>
<th>IXE (n = 49)</th>
<th>ADA (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.3 ± 11.5</td>
<td>46.3 ± 11.3</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>30 (61.2)</td>
<td>33 (64.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.5 ± 7.3</td>
<td>30.2 ± 8.7</td>
</tr>
<tr>
<td>Duration of symptoms since PsO diagnosis (years)</td>
<td>17.0 ± 10.5</td>
<td>15.0 ± 11.3</td>
</tr>
<tr>
<td>Duration of symptoms since PsA diagnosis (years)</td>
<td>7.0 ± 7.4</td>
<td>5.7 ± 6.2</td>
</tr>
<tr>
<td>PASI</td>
<td>22.9 ± 10.5</td>
<td>20.5 ± 7.3</td>
</tr>
<tr>
<td>sPGA</td>
<td>3.6 ± 0.7</td>
<td>3.6 ± 0.7</td>
</tr>
<tr>
<td>Percentage BSA</td>
<td>41.2 ± 24.1</td>
<td>32.5 ± 19.3</td>
</tr>
<tr>
<td>Fingernail NAPSI ≥ 1, n (%)</td>
<td>37 (75.5)</td>
<td>41 (80.4)</td>
</tr>
<tr>
<td>Fingernail NAPSI</td>
<td>26.1 ± 21.6</td>
<td>23.3 ± 18.5</td>
</tr>
<tr>
<td>Fingernail NAPSI &gt; 16, n (%)</td>
<td>21 (42.9)</td>
<td>24 (47.1)</td>
</tr>
<tr>
<td>Fingernail NAPSI &gt; 40, n (%)</td>
<td>10 (20.4)</td>
<td>7 (13.7)</td>
</tr>
<tr>
<td>Itch NRS</td>
<td>6.5 ± 2.5</td>
<td>7.6 ± 1.8</td>
</tr>
<tr>
<td>DLQI</td>
<td>16.9 ± 7.3</td>
<td>16.7 ± 6.4</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>24.2 ± 15.7</td>
<td>23.9 ± 15.5</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>12.4 ± 9.7</td>
<td>13.0 ± 11.0</td>
</tr>
<tr>
<td>CRP level (mg/L)</td>
<td>14.5 ± 21.7</td>
<td>17.6 ± 28.9</td>
</tr>
<tr>
<td>Concomitant MTX use, n (%)</td>
<td>25 (51.0)</td>
<td>28 (54.9)</td>
</tr>
</tbody>
</table>

Unless indicated otherwise, data are presented as mean ± SD.

ADA = Adalimumab; BMI = Body Mass Index; BSA = Body surface area; CRP = C reactive protein; DLQI = Dermatology Life Quality Index; MTX = Methotrexate; NAPSI = Nail Psoriasis Severity Index; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; PsA = Psoriatic arthritis; PsO = Plaque psoriasis; SD = Standard deviation; sPGA = Static Physician Global Assessment.

represented in Figure 1. Baseline demographics and disease characteristics were mostly balanced between the IXE and ADA groups (Table 1). Totals of 51.0% and 54.9% of IXE- and ADA-treated patients, respectively, had concomitant methotrexate (MTX) use at baseline, which was permitted throughout the study.

Figure 1. Schematic representation of moderate-to-severe psoriasis and nail psoriasis frequency in the SPIRIT-H2H patient population. Venn diagrams show the proportion of patients with moderate-to-severe PsO and nail PsO (NAPSI ≥ 1) in the IXE (n = 283) and ADA (n = 283) groups of the entire SPIRIT-H2H population at baseline.

ADA = Adalimumab; IXE = Ixekizumab; Mod-sev = Moderate-to-severe; NAPSI = Nail Psoriasis Severity Index; PsA = Psoriatic arthritis; PsO = Plaque psoriasis.
Efficacy on Skin, Nails, and Joints

In the subgroup of patients with active PsA and moderate-to-severe PsO at baseline, a significantly higher proportion of patients treated with IXE versus ADA simultaneously achieved the primary endpoint, ACR50 and PASI100, at W24 (40.8% versus 17.6%, P = 0.015) and W52 (38.8% versus 17.6%, P = 0.026); statistically significant differences were observed as early as W8 (Figure 2).

Complete skin clearance (PASI100 response) was achieved by a significantly higher proportion in the IXE versus ADA group at W24 (59.2% versus 27.5%, P = 0.002) and W52 (59.2% versus 25.5%, P = 0.001); significant differences were observed as early as W4 (the first PASI assessment) and maintained throughout the study (Figure 3A). Likewise, PASI90 response was significantly greater in IXE- versus ADA-treated patients at all time points starting at W4, except at W32 (Figure 3B). IXE- versus ADA-treated patients had more rapid PASI75 responses with a significantly higher proportion achieving PASI75 from W4 to W16, and numerically, but not significantly (except for W40), more patients achieving PASI75 through W52 (Figure 3C).

With regard to joint outcomes, no significant differences were observed in ACR50 at W24 and in ACR20, ACR50, or ACR70 responses between IXE- and ADA-treated patients through W52 (Table 2).

Nail PsO was prevalent in patients with active PsA and moderate-to-severe PsO, affecting 75.5% (n = 37) and 80.4% (n = 41) of IXE- and ADA-treated patients, respectively, at baseline (fingernail NAPSI ≥ 1). Baseline demographics and disease characteristics of patients with nail PsO were balanced between the IXE and ADA groups (data not shown). Complete clearance of fingernail PsO occurred in 75.7% of IXE- versus 51.2% of ADA-treated patients at W24 (P = 0.035), and a numerically higher proportion of IXE- versus ADA-treated patients had a NAPSI = 0 response at all time points through W52 (Figure 4A). The mean change from baseline in fingernail NAPSI score indicated a more rapid decrease overall and a statistically larger difference for IXE- versus ADA-treated patients at W40, and numerically greater for all other time points through W52 (-21.9 versus -20.9, P = 0.583) (Figure 4B).

Patient-reported Outcomes

The baseline DLQI scores for the subgroup of patients with active PsA and moderate-to-severe PsO were 16.9 (standard deviation [SD] ± 7.3) and 16.7 (SD ± 6.4) for IXE- and ADA-treated patients, respectively, which was reflective of the high disease burden of this subgroup (Table 1). In the IXE versus ADA group, significantly more patients reported no or only minimal impact of skin disease on their QoL (DLQI 0,1) at W24 (59.2% versus 33.3%, P = 0.016) and numerically more at W52 (55.1% versus 37.3%, P = 0.108) (Figure 5A). IXE-versus ADA-treated patients had a more rapid mean reduction in DLQI score from baseline. The mean change in DLQI was consistently greater in the IXE- versus ADA-treated patients and was statistically greater at W4 through W16 (Figure 5B).

The mean change in Itch NRS score from baseline and complete resolution of itch (Itch NRS = 0) were numerically higher (except for the mean change in Itch NRS score from baseline at W52, which was numerically equal) but not significantly different in the IXE versus ADA group at all time points through W52 (Figure 5C and D).

Safety

The frequency of TEAEs was similar in patients receiving IXE versus ADA (59.2% versus 58.8%) (Table 3); all TEAEs
Figure 3. Skin outcomes through Week 52. Percentage of patients with PsA and moderate-to-severe PsO achieving (A) PASI100, (B) PASI90, and (C) PASI75. IXE versus ADA: * P ≤ 0.05, ** P ≤ 0.01, *** P ≤ 0.001.

ADA = Adalimumab; IXE = Ixekizumab; PASI = Psoriasis Area and Severity Index; PsA = Psoriatic arthritis; PsO = Plaque psoriasis.

ADA = Adalimumab; IXE = Ixekizumab; PASI = Psoriasis Area and Severity Index; PsA = Psoriatic arthritis; PsO = Plaque psoriasis.

ADA = Adalimumab; IXE = Ixekizumab; PASI = Psoriasis Area and Severity Index; PsA = Psoriatic arthritis; PsO = Plaque psoriasis.
Table 2. Joint outcomes at Weeks 24 and 52

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th></th>
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<th>Week 52</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IXE</td>
<td>ADA</td>
<td>Treatment</td>
<td>IXE</td>
<td>ADA</td>
</tr>
<tr>
<td></td>
<td>(n = 49)</td>
<td>(n = 51)</td>
<td>difference</td>
<td>(n = 49)</td>
<td>(n = 51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IXE versus ADA</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td>21 (42.9)</td>
<td>17 (33.3)</td>
<td>9.5 (-9.4, 28.5)</td>
<td>0.411</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>ACR50</td>
<td>29 (59.2)</td>
<td>28 (54.9)</td>
<td>4.3 (-15.1, 23.7)</td>
<td>0.691</td>
<td>27 (55.1)</td>
</tr>
<tr>
<td>ACR20</td>
<td>37 (75.5)</td>
<td>40 (78.4)</td>
<td>-2.9 (-19.4, 13.6)</td>
<td>0.814</td>
<td>36 (73.5)</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values are presented as n (%).

^a P value: IXE versus ADA

ACR = American College of Rheumatology; ADA = Adalimumab; CI = Confidence intervals; IXE = Ixekizumab.

Figure 4. Clinical response rate for Fingernail PsO endpoints through Week 52. Graphs depict results for patients with moderate-to-severe PsO, PsA and a fingernail NAPSI ≥ 1 score at baseline. (A) Percentage of patients achieving fingernail NAPSI = 0 through Week 52. (B) Mean change in fingernail NAPSI score from baseline through Week 52. IXE versus ADA: * P ≤ 0.05, **P ≤ 0.01.

ADA = Adalimumab; IXE = Ixekizumab; NAPSI = Nail Psoriasis Severity Index; PsA = Psoriatic arthritis; PsO = Plaque psoriasis.
Figure 5. Clinical response rate for quality-of-life endpoints through Week 52. Graphs depict results for patients with PsA and moderate-to-severe PsO at baseline. (A) Percentage of patients achieving DLQI (0,1) through Week 52. (B) Mean change from baseline in DLQI score through Week 52. (C) Percentage of patients achieving Itch NRS = 0 through Week 52. (D) Mean change from baseline in Itch NRS score through Week 52. IXE versus ADA: * P ≤ 0.05, ** P ≤ 0.01.

ADA = Adalimumab; DLQI = Dermatology Life Quality Index; IXE = Ixekizumab; NRS = Numeric Rating Scale; PsA = Psoriatic arthritis; PsO = Plaque psoriasis.

in the IXE group and 86.7% in the ADA group were mild or moderate, while 13.3% in the ADA group were severe. The TEAEs are consistent with the known safety profiles of both drugs. The frequency of serious AEs (SAEs) was lower in IXE- versus ADA-treated patients (0.0% versus 9.8%) and a lower proportion of patients in the IXE group discontinued due to an AE compared with ADA group (2.0% versus 7.8%). No deaths occurred during the study.

Conclusions

This subgroup analysis focused on the biologic-naïve patients with active PsA and moderate-to-severe PsO at baseline in the SPIRIT-H2H trial, which demonstrated higher efficacy of IXE versus ADA in patients with active PsA and PsO, and determined that IXE is also more efficacious than ADA for simultaneously achieving ACR50 and PASI100 at W24 and W52 in this subgroup [18,19]. Overall, IXE-treated patients demonstrated higher responses for resolution of skin and nail manifestations of PsO versus ADA-treated patients and comparable response rates regarding improvement in joint symptoms. Importantly, while anti-TNF biologics have previously been recommended as the first-line biologic to treat patients with PsA and PsO, these results indicate that IXE is as good as, if not better than, ADA in treating patients with active PsA and moderate-to-severe PsO [24].

Moderate-to-severe PsO can have considerable negative effects on patients QoL, and the burden of disease can be further compounded by the presence of nail PsO and comorbid PsA. The IXE group had significantly more patients achieving DLQI (0,1) at W24 and numerically more through W52 compared with the ADA group, indicating that rapid and sustained skin clearance had important and clinically meaningful effects on QoL for patients with active PsA and moderate-to-severe PsO.
Table 3. Safety outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>IXE (N = 49)</th>
<th>ADA (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE</td>
<td>29 (59.2)</td>
<td>30 (58.8)</td>
</tr>
<tr>
<td>TEAE by severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>17 (34.7)</td>
<td>15 (29.4)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (24.5)</td>
<td>11 (21.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAEa</td>
<td></td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Treatment discontinuation due to AE</td>
<td>1 (2.0)</td>
<td>4 (7.8)</td>
</tr>
</tbody>
</table>

AE of special interest

| Infections                           | 13 (26.5)    | 18 (35.3)    |
| Serious infectionsb                   | 0            | 1 (2.0)      |
| Injection site reactionsc             | 2 (4.1)      | 0            |
| Allergic/hypersensitivity reactionsd  | 2 (4.1)      | 2 (3.9)      |
| Cerebrocardiovascular eventsd         | 0            | 1 (2.0)      |
| Depression                            | 1 (2.0)      | 0            |

Data are presented as n (%).

aData were acute abdomen disorder (n = 1), pyrexia (n = 1), cellulitis (n = 1), polyneuropathy (n = 1), and peripheral artery occlusion and necrosis ischemic vascular disorder (n = 1).

bSerious infection was cellulitis.
cDefined by High Level Term (HLT).
dNo confirmed anaphylaxis reported after medical review.

eCerebro-cardiovascular events are defined using terms from the following subcategories: cardiovascular death, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, hospitalization for serious arrhythmia, hospitalization for hypertension, resuscitated sudden death, cardiogenic shock due to myocardial infarction, coronary revascularization procedure, neurologic-stroke, and peripheral vascular events.

ADA = Adalimumab; AE = Adverse event; IXE = Ixekizumab; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event.

Nail PsO can substantially compromise patients’ daily activities by causing pain and impairing hand mobility and is a particularly difficult to treat manifestation of PsO [8]. Improvement and clearance of nail PsO is a long process, partially due to the slow growth rate of nails, and consequently, efficacy cannot be evaluated before 12 weeks of treatment [25]. In our subgroup analysis, the proportion of patients experiencing nail PsO was higher than in other moderate-to-severe PsO clinical trial populations as all patients had concomitant active PsA, which is associated with higher rates of nail PsO than PsO [26,27]. Notably, IXE treatment resulted in a more rapid increase overall in clearance of nail PsO than ADA, with significantly more IXE- versus ADA-treated patients demonstrating complete clearance of nail PsO at W24.

Previously published results from the IXORA-S trial have demonstrated that IXE is superior to ustekinumab, an anti-IL-12/23 biologic, in clearance of nail PsO at W24 [26]. Similarly, in the IXORA-R head-to-head trial comparing IXE with guselkumab (GUS), an anti-IL-23p19 biologic, IXE was superior to GUS in clearance of nail PsO at W24 [28]. The VOYAGE-1 and -2 trials demonstrated superiority of GUS to ADA in achieving clear/almost clear skin at W16; however, post hoc analysis demonstrated that improvements in nail PsO from baseline were higher for ADA versus GUS at W16, which suggests that the different methods of action of biologics may result in differing effects on specific PsO disease domains, such as nail PsO [29–31]. Importantly, our analysis of the SPIRIT-H2H subgroup with active PsA and moderate-to-severe PsO demonstrates that IXE has higher efficacy than ADA in achieving complete clearance of the skin and nails at W24. Overall, these and previously published results demonstrate the consistent high efficacy of IXE in achieving clearance of nail PsO. This is supported by multiple recent network meta-analyses, which report that IXE had the highest ranking among approved biologics (and small molecules in one network meta-analysis) for the treatment and/or clearance of nail PsO [32–34].

Of note, > 50% of patients in our subgroup analysis had concomitant MTX use at baseline. Previously published studies have indicated that concomitant MTX treatment improves the efficacy of ADA and other anti-TNF biologics in treating rheumatoid arthritis, but the results regarding the effect of this combined therapy for PsA have been inconclusive [35–38]. It has been suggested that in the overall SPIRIT-H2H study population, concomitant treatment with MTX increases the proportion of ADA-treated patients achieving simultaneous ACR50 and PASI100, or NAPSI =
0 at W52 but does not have a response-modifying effect in IXE-treated patients [39]. Therefore, it is possible that the proportion of ADA-treated patients achieving simultaneous ACR50 and PASI100, or clearance of nail PsO in our subgroup analysis is higher than would be observed in patients receiving ADA monotherapy.

The safety profiles of both IXE and ADA were consistent with previous clinical trials and the prescriber information for both drugs. The ADA group had numerically more SAEs (there were no SAEs in the IXE group) and treatment discontinuations due to AEs, which is consistent with previously published safety data from the overall SPIRIT-H2H trial [18,19].

The limitations of this study include the open-label design, which may have biased the outcome assessments. Another limitation is that while the data show clinically meaningful differences, the sample size was small and this post hoc analysis was not powered to demonstrate statistical differences between these subgroups.

In conclusion, this subgroup analysis demonstrated that IXE- versus ADA-treated patients achieved significantly greater simultaneous PASI100 and ACR50 responses through W52 and confirmed IXE as an efficacious and safe treatment for patients with active PsA and moderate-to-severe PsO. Additionally, comparison of the results of this analysis with those of other studies confirm the efficacy of IXE in treating nail PsO in patients with moderate-to-severe PsO, irrespective of concomitant active PsA [26-28]. These results increase awareness of available treatment options and inform evidence-based clinical decisions for patients with active PsA and moderate-to-severe PsO.

Acknowledgements

The authors would like to thank Gabrielle Stack, PhD, a medical writer and employee of Eli Lilly and Company, for writing and editorial support.

References


Introduction: Pain is experienced by most patients with hidradenitis suppurativa (HS) and has a severe impact on their quality of life. Its management still presents a challenge. Adalimumab, a TNF-α antagonist, has shown promising results in HS-related pain reduction.

Objectives: To aggregate and synthesize all existing evidence regarding the effect of adalimumab on HS-associated pain.

Methods: We identified original controlled and uncontrolled studies with participants receiving adalimumab, which included change in pain score post-treatment compared to baseline as an endpoint. We searched MEDLINE, ScienceDirect, the Cochrane Library, ClinicalTrials.gov and International Clinical Trials Registry Platform. The primary endpoint of our study was the mean change (continuous variable) of pain scores at week 12 compared to baseline.

Results: We performed a meta-analysis of 4 randomized controlled trials (282 patients in the intervention group and 266 patients in the control group). Adalimumab brought about a 0.418 reduction in mean pain score at its worst with 95% CI [−0.588, −0.248] and \( P = 0.000 \) at 12 weeks after treatment commencement. Four more studies were included in a qualitative synthesis, 2 of which reported statistically significant reduction in pain scores at week 12.

Conclusions: Adalimumab could be prescribed more readily in cases of HS associated with significant pain.
Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease (of the terminal hair follicle) that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly in the axillary, inguinal, and anogenital regions [1]. Pain is experienced by the majority of HS patients [2–4]. HS-related pain is greater than the one associated with other skin diseases, such as eczema, psoriasis, skin tumors and acne, and constitutes one of the major reasons for the seriously impaired patient quality of life [4,5]. Among other things, pain is responsible for the poor sleep quality, impaired general activity, negatively affected inter-personal relationships and reduced life enjoyment of this population [2,6]. Perception of HS pain is influenced by depression and anxiety, which are frequent comorbidities, as well as by gender and age [3].

HS-related pain derives from deep-seated skin lesions and is of two types: acute/episodic, attributed to disease flares (newly formed and/or old recurring nodules and abscesses), and chronic, which is the result of longstanding inflamed lesions such as sinuses, dermal nodules and contracted scars [7–9]. Acute-pain relief is usually facilitated through abscess rupture or acute surgical interventions [7,9]. HS pain is most commonly described as “shooting” (83%), “itchy” (79%) and “blinding” (75%) and is more intense when more anatomic areas are involved or when disease is more severe (Hurley stage III) [3]. The 3 most common self-reported pain aggravators are friction from tight clothing (47%), heat (40%) and stress (13%) [10].

According to Ring et al HS patients tend to desperately seek for ways to alleviate their pain [10]. The majority of them make use of analgesics (77%) [11]. Common pain relief strategies include non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol received either topically or systemically, as well as cold baths and wraps [9,10,12]. It is worth noting that this data has originated from European studies. When pain is very severe, careful administration of opioids in collaboration with a pain specialist should be considered [9,13]. Self-reported use of tramadol was 37% in a 2016 study and opioids were reported the most efficient in offering relief [11]. Other options may include antidepressants, anticonvulsants, specialist psychological support and patient support groups [9,12].

Only a small number of studies have looked into the prevalence and impact of pain or strategies for its alleviation in HS populations [3,14]. What is more, it seems that the analgesics most commonly used by HS patients are inadequate [10]. Adalimumab, a tumor necrosis factor antagonist, has been approved for the treatment of moderate-to-severe HS, based on the results of 2 clinical trials (PIONEER I and II) [15,16]. A number of studies have reported that adalimumab can effectively reduce pain. This is the first systematic review and meta-analysis to aggregate and synthesize all existing data concerning adalimumab efficacy in alleviating HS-related pain.

Methods

Study Design

This systematic review aimed at examining the effect of adalimumab on HS-related pain. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered with PROSPERO (ID: CRD42021229190).

Eligibility Criteria

To answer the research question, we identified original studies with participants receiving adalimumab, which included change in pain scores compared to baseline as an endpoint. We imposed no restrictions on adalimumab dose, language and year of publication and publication status. We included both clinical trials and controlled and uncontrolled observational studies in our review.

Literature Search

A comprehensive electronic search of 5 databases was conducted, namely MEDLINE, ScienceDirect, the Cochrane Library, ClinicalTrials.gov and International Clinical Trials Registry Platform, from November 5–20, 2020, to source studies pertaining to the research question. We also searched Google Scholar and the archives of the major recent dermatology conferences to identify gray literature. Finally, we contacted AbbVie, the major sponsor of adalimumab trial projects, requesting unpublished material. The “Reference” section of manuscripts relevant to the research question was hand-searched, to maximize the sensitivity of our search. As this study was a review of existing research projects, neither informed consent nor ethics approval was required.

The comprehensive database search was performed independently by 2 authors (A.T. and E.S.). We used the following free-text terms for the MEDLINE database search: (hidradenitis suppurativa) OR (acne inversa) AND (adalimumab) OR (biologic) OR (Humira®) OR (anti-TNF) OR (monoclonal antibody) AND (pain) OR (skin pain) OR (ache). Appropriate modifications were applied to the above search strategy, so that it would comply with the search rules of the rest of used databases.

Study Selection

After removing duplicates, A.T. and E.S. initially, independently, read titles and abstracts to eliminate records out of the scope of this review. They subsequently went through the full details of each record and settled disputes through consensus, having a set of predetermined inclusion and
exclusion criteria as a guide. Studies adhering to the following criteria were considered for inclusion: 1) trial or observational study, controlled or not, 2) recruited patients with a clinical diagnosis of HS, 3) patients (all of them or intervention arm) received adalimumab subcutaneously, 4) pain intensity was assessed with a validated pain measuring scale at baseline and 12 weeks after commencing treatment, 5) change in pain scores and/or proportion of patients achieving a certain reduction in such scores was documented, 6) included patients were adults of any age, gender and background population. A study was excluded if it included: 1) non-human subjects, 2) pregnant or lactating females. All selected studies were included in the qualitative synthesis, but only controlled ones were included in the quantitative synthesis.

Data Extraction
Eligible studies were subjected to data extraction using a pre-formulated extraction sheet. This process was performed independently by two researchers (A.T. and E.S) and any discrepancies were settled through discussion and agreement. The following data was retrieved from each one of the selected studies: general characteristics (study identifier, ClinicalTrials.gov identifier, study design, phase, number of study sites, countries included, study period, funding, inclusion criteria, exclusion criteria, intervention, comparator, follow-up duration, primary endpoint(s), secondary endpoints) and outcome data.

Data Items
Pain intensity is measured with scales assigning increasing value to increasing pain intensity. In dermatology, both generic visual analogue scales (VAS) and specific tools, such as the Patient’s Global Assessment of Skin Pain Numeric Rating Scale (NRS), are commonly used [17]. The former represents a 100 mm-long scale, with 0 corresponding to “no pain” and 100 to “worst possible pain” [17]. NRS consists of successive numbers (the actual length of the scale is not important), usually presented on a horizontal linear configuration, from 0 (no pain) to 5 or 10 (worst possible pain) [17]. The patient is asked to mark the point/length that best corresponds to his/her pain intensity and this value is documented [17]. Mean change and the proportion of patients achieving a certain score reduction are common efficacy endpoints. NRS30 is a 30% and at least 1 unit reduction in the PGA skin pain NRS score compared to baseline. We imposed no restrictions to our search regarding the pain measuring tools used, on the basis that VAS data can be turned into NRS data through dividing by ten. The primary endpoint of our study was mean change (continuous variable) of pain scores at week 12 compared to baseline. In the absence of published statistical measures needed, we contacted authors and requested said data. Secondary endpoint was the percentage of patients achieving NRS30 (dichotomous variable) at week 12. The 12-week timeframe was chosen, as it is a sensible and widely used milestone regarding assessment of biologics’ efficacy both in research and clinical practice.

Risk of Bias Assessment
Two researchers (A.T. and E.S) independently used the Cochrane risk-of-bias tool [18] to assess the risk of bias for included randomized controlled clinical trials. Any disagreements were resolved through consensus. Seven items were rated as “high risk,” “low risk,” or “unclear risk” of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other sources of bias. Non-randomized and/or uncontrolled studies were assessed through the Methodological Index for Non-randomized studies (MINORS) [19]. Studies were considered low risk if all items were reported and adequate. Observational studies were evaluated through the National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies. Fourteen individual points were thus examined and an overall quality rating of good, fair, or poor was allocated to each study [20].

Statistical analysis
We performed all statistical analyses with Comprehensive Meta Analysis software (Comprehensive Meta-Analysis Version 3, Borenstein M, Hedges I, Higgins J, Rothstein H, Biostat). Confidence intervals, P values, standard deviations (SD) and other statistical measures were mentioned, if available. In the opposite case, authors were contacted and if they did not respond, results were described only narratively. The primary goal of this systematic review was to culminate in a meta-analysis – quantitative synthesis – of the main outcome measure. The principal summary measure used for the analysis of the primary endpoint was the mean difference in pain scores between baseline and week 12. A decrease in the mean of pain scores meant that adalimumab had a positive effect on pain. Associated 95% confidence intervals (CI) were estimated and differences were considered significant when P ≤ 0.05 (two-tailed). The secondary endpoint was analyzed through descriptive statistics (frequencies). The presence of heterogeneity across studies was examined through the I² statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). In case heterogeneity was substantial or considerable (≥30%), the random effects model was used. In the opposite case, the fixed effects model was used. A funnel plot was created to check for publication bias.
Results

Study Selection and Characteristics

Our search and screening process (Figure 1) culminated in 8 studies eligible for inclusion. Basic study characteristics are presented in Table 1. All studies were published in English. More than 1 publication was identified for 3 studies [14,21–23], in which case, one of those was chosen as the study identifier based on its relevance to this review’s primary endpoint. Four of the included studies were randomized controlled trials (RCTs)[14,23,24], 2 were prospective open-label uncontrolled trials [25,26], 1 was a retrospective cross-sectional study [27] and one was a post-marketing observational study [28,29]. A total of 863 participants with a mean age of 36.51 (SD = 11.59) years received either adalimumab subcutaneous injection (489 participants) or placebo (374 participants). The dosing of adalimumab was not consistent across all 8 studies or all study arms. Three studies [14,24,25] examined the efficacy of 40 mg of adalimumab administered every other week and 4 studies [14,23,26–28] evaluated the efficacy of 40 mg of adalimumab administered weekly. Alternate weekly dosing was also investigated in the second period of the 2 main phase III RCTs (PIONEER I and II), on which drug approval was based [23]. In the second period of a recent phase III study, alternate weekly administration of 80 mg of adalimumab was also assessed [26]. In most studies [14,23,26–28] an introductory dosage of 160 mg at week 0, 80 mg at week 2, and 40 mg at week 4 was administered prior to maintenance treatment. A different introductory regimen was employed in 2 studies [24,25] (160 mg at week 0, 80 mg at week 1, 40 mg at week 4, and 80 mg at week 0 respectively). Baseline characteristics of participants are presented in Table 2.

![Figure 1. Flow diagram of study selection based on the 2009 PRISMA statement format.](image-url)
### Table 1. Study Characteristics

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<td>Inclusion criteria</td>
<td>Healthy adults, able to administer subcutaneous injections, negative chest X-ray and PPD test or completed anti-tuberculosis therapy</td>
<td>≥18 years, moderate to severe HS and ≥1 of: ≥1-year duration, multiple ER or doctor visits, &gt;5/year triamcinolone injections, failed retinoids and antibiotics, reconstructive surgery, normal laboratory values</td>
<td>18-99 years, HS for at least 1 year and stable for at least 2 months, at least 2 anatomic areas, one at least Hurley Stage II or III, AN count ≥3, inadequate response to at least 90 days of antibiotics for HS</td>
<td>18-99 years, HS for at least 1 year and stable for at least 2 months, at least 2 anatomic areas, one at least Hurley Stage II or III, AN count ≥3, inadequate response to at least 90 days of antibiotics for HS</td>
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<td>Exclusion criteria</td>
<td>Prior anti-TNF treatment, unstable antibiotic therapy for HS, required medication washouts for other HS treatments, prior exposure to Tysabri® (natalizumab), recent infection requiring treatment, significant medical events or conditions, pregnancy or breast-feeding or considering becoming pregnant during the study, history of cancer, except successfully treated skin cancer, recent history of drug or alcohol abuse</td>
<td>Pregnancy, lactation, planning pregnancy, adalimumab allergy, systemic anti-inflammatory medication except NSAID and low-dose systemic steroids, HIV, HBV or HCV seropositive, serious infections in previous 3 months, mycobacterial or opportunistic infection within prior 6 months, lymphoproliferative disease, lymphadenopathy or splenomegaly, malignancy within 5 years except fully excised BCC, severe organ failure, solid organ transplant, granulomatous infection</td>
<td>Prior adalimumab or other anti-TNF treatment, antibiotics for HS within previous 28 days, oral analgesics for HS within past 14 days, oral opioid or non-stable dose of non-opioid analgesics for reason unrelated with HS within past 14 days</td>
<td>Prior adalimumab or other anti-TNF treatment, non-stable dose of permitted antibiotics for HS within previous 28 days, oral analgesics for HS within past 14 days, oral opioid or non-stable dose of non-opioid analgesics for reason unrelated with HS within past 14 days</td>
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<td><strong>Intervention</strong></td>
<td>Period 1: Adalimumab, subcutaneous injection, 160 mg at week 0, 80 mg at Week 2, and 40 mg weekly starting at Week 4 through Week 15. Or 80 mg at Week 0 and 40 mg every other week starting at Week 1 through Week 15. Period 2: 36 weeks, open label, adalimumab 40 mg every other week</td>
<td>Adalimumab subcutaneous injection, 160 mg at Week 0, followed by 80 mg at Week 1, and 40 mg at alternate weeks until Week 12</td>
<td>Period 1: Adalimumab, subcutaneous injection, 160 mg at Week 0, 80 mg at Week 2, 40 mg every week from Week 4 to Week 12. Period 2: prior placebo -&gt; adalimumab 40 mg every week until week 35, prior adalimumab -&gt; placebo every week, adalimumab 40 mg every week or adalimumab 40 mg every other week</td>
<td>Period 1: Adalimumab, subcutaneous injection, 160 mg at Week 0, 80 mg at Week 2, 40 mg every week from Week 4 to Week 12. Period 2: prior placebo -&gt; adalimumab 40 mg every week until week 35, prior adalimumab -&gt; placebo every week, adalimumab 40 mg every week or adalimumab 40 mg every other week</td>
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<td><strong>Primary endpoint(s)</strong></td>
<td>Proportion of patients achieving an HS-PGA score of clear, minimal, or mild with at least a 2-grade improvement relative to baseline at Week 16</td>
<td>Proportion of patients achieving decrease of 50% from baseline in the HSSI score after 12 weeks of treatment</td>
<td>Percentage of participants achieving HiSCR at Week 12</td>
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<td><strong>Secondary endpoints</strong></td>
<td>Proportion of patients achieving clinical response at Weeks 2, 4, 8, and 12 and all visits (period 2), HS-PGA score of clear, minimal, or mild, mean change in MSS, mean percentage of improvement in abscesses, draining fistulas, or inflammatory nodules, mean change in C-reactive protein levels, mean change in DLQI score, total work productivity impairment at Week 16. Post hoc analysis: proportion of patients achieving 30% or greater reduction and a 10-mm or greater absolute reduction in pain Visual Analogue scale score</td>
<td>Difference from baseline at 12 weeks in pain measured by a Visual Analog Scale, DLQI, and PGA of disease severity, number of patients with a &gt;30 and &gt;50% disease activity at 12 weeks, adverse events</td>
<td>Percentage of participants achieving AN count 0, 1 or 2, NRS30 – At worst at week 12, change of MSS at week 12</td>
<td>Percentage of participants achieving AN count 0, 1 or 2, NRS30 – At worst at week 12, change of MSS at week 12</td>
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**Table 1. Study Characteristics (Continued)**

*HS = hidradenitis suppurativa; ER = emergency room; AN count = abscess and inflammatory nodule count; NSAID = non-steroidal anti-inflammatory drug; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HS-PGA = Hidradenitis suppurativa – Physician’s Global Assessment; HSSI = Hidradenitis Suppurativa Severity Index; HiSCR = Hidradenitis Suppurativa Clinical Response; MSS: Modified Sartorius Score; DLQI = Dermatology Life Quality Index; NRS30 = at least 30% and 1 unit reduction in pain numeric rating scale score.*
Table 1. Study Characteristics (Continued)

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<td>18–99 years, HS for at least 6 months &amp; stable for at least 2 months, ≥2 anatomic areas, one at least Hurley Stage II or III, AN count ≥3</td>
<td>18–99 years, HS diagnosis, receiving Adalimumab according to the Summary of Product Characteristics, willingness to sign informed consent</td>
<td>≥18 years, Hurley stage II or III HS for at least 6 months, at least 4 weeks of wash-out for previous treatments, females instructed to use contraception</td>
<td>≥18 years, diagnosis of HS, AN count ≥ 3 at baseline, ≥ 1 year of treatment with adalimumab</td>
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<td>Exclusion criteria</td>
<td>Prior adalimumab or other anti-TNF treatment, other skin condition impeding HS assessment, antibiotics for HS other than a stable dose of doxycycline or minocycline for past 28 days, topical treatments or oral analgesics for HS within past 14 days, systemic treatment for HS within past 28 days</td>
<td>Prior biologic treatment discontinued &lt;6 months before the baseline visit Patient not able to understand the language of provided patient questionnaires, history of non-compliance with medication or a medical history that could enhance non-compliance with medication</td>
<td>Prior biologic treatment, conventional HS treatment within past 4 weeks, chronic or recurrent infections, allergy to study drug, serious health problems, pregnancy and breastfeeding, untreated or latent tuberculosis, cancer history, drug or alcohol abuse</td>
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<td>Adalimumab according to Summary of Product characteristics</td>
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<td><strong>Primary endpoint(s)</strong></td>
<td>Percentage of participants achieving HiSCR at Week 12</td>
<td>Change in DLQI score from baseline at Week 12</td>
<td>Change in Sartorius and Hurley scores at Weeks 12 and 24</td>
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<td><strong>Secondary endpoints</strong></td>
<td>Percentage of participants achieving AN count 0, 1 or 2 at Week 12, NRS30 – At Worst at Week 2, change of MSS at Weeks 2, 4, 8 &amp; 12</td>
<td>Change from baseline: of pain Numeric Rating Scale – at worst and on average at Weeks 4, 12 and 24, of DLQI at Weeks 4 and 24, of EQ-5D Questionnaire responses, EQ-5D VAS Score, HSIA Overall Score, WPAI-SHP score at Weeks 4, 12 &amp; 24, achievement of HiSCR at Weeks 4, 12 &amp; 24</td>
<td>Change in VAS pain score at Weeks 12 and 24, self-reported days with lesions between visits, DLQI and evaluation of scarring [Manchester post-inflammatory scar scoring and Physician Global Assessment scar scoring], documentation of adverse events</td>
<td>Every 12 weeks: number of patients achieving HiSCR of ≥ 50% reduction in inflammatory lesion count, number of flares, mean time between flares, Hidradenitis Suppurativa IHS4, pain VAS and lesion count. Additionally, DLQI was assessed to measure quality of life (QoL) every 24 weeks.</td>
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</tbody>
</table>

HS = hidradenitis suppurativa; AN count = abscess and inflammatory nodule count; HiSCR = Hidradenitis Suppurativa Clinical Response; DLQI = Dermatology Life Quality Index; NRS30 = at least 30% and 1 unit reduction in pain numeric rating scale score; MSS = Modified Sartorius Score; EQ-5D = instrument for evaluation of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; VAS = Visual Analogue Scale; HSIA = Hidradenitis Suppurativa Impact Assessment; WPAI-SHP = Work Productivity and Activity Impairment – Specific Health Problem; HiSCR: Hidradenitis Suppurativa Clinical Response; IHS4 = International Hidradenitis Suppurativa Severity Score System.
Table 2. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>154</td>
<td>10</td>
<td>307</td>
<td>326</td>
<td>15</td>
<td>10</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Adalimumab (Ada) (n, %)</td>
<td>103 (66.88)</td>
<td>10 (100)</td>
<td>153 (49.84)</td>
<td>163 (50)</td>
<td>15 (100)</td>
<td>10 (100)</td>
<td>15 (71.43)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Placebo (Pbo) (n, %)</td>
<td>51 (33.12)</td>
<td>0</td>
<td>154 (50.16)</td>
<td>163 (50)</td>
<td>0</td>
<td>0</td>
<td>6 (28.57)</td>
<td>0</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>f: 74 (48.05)</td>
<td>f: 7 (70.0)</td>
<td>f: 91 (29.64)</td>
<td>f: 108 (33.13)</td>
<td>f: 2 (13.3)</td>
<td>f: 7 (70)</td>
<td>f: 12 (57.14)</td>
<td>f: 14 (70)</td>
</tr>
<tr>
<td></td>
<td>m: 29 (18.83)</td>
<td>m: 3 (30.0)</td>
<td>m: 62 (20.20)</td>
<td>m: 55 (16.87)</td>
<td>m: 13 (86.7)</td>
<td>m: 3 (30)</td>
<td>m: 3 (14.29)</td>
<td>m: 6 (30)</td>
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<tr>
<td>Placebo</td>
<td>f: 36 (23.38)</td>
<td>0</td>
<td>f: 105 (34.20)</td>
<td>f: 113 (34.67)</td>
<td>0</td>
<td>0</td>
<td>f: 5 (23.81)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>m: 15 (9.74)</td>
<td></td>
<td>m: 49 (15.96)</td>
<td>m: 50 (15.34)</td>
<td></td>
<td></td>
<td>m: 1 (4.76)</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean, SD/95%CI)</td>
<td>Ada: 35.6 (11.6)</td>
<td>32.6 (11.14)</td>
<td>Ada: 36.2 (10.83)</td>
<td>Ada: 34.9 (9.96)</td>
<td>42.1 (6.94)</td>
<td>42.7 (11.47)</td>
<td>Ada: 38.7 (30.9–46.4)</td>
<td>35.1 (12)</td>
</tr>
<tr>
<td></td>
<td>Pbo: 37.8 (12.1)</td>
<td></td>
<td>Pbo: 37.8 (11.33)</td>
<td>Pbo: 36.1 (12.18)</td>
<td></td>
<td></td>
<td>Pbo: 40.2 (25.8–54.5)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity (n, %)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>Ada: 73 (47.4)</td>
<td>5 (50)</td>
<td>Ada: 116 (37.79)</td>
<td>Ada: 143 (43.87)</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Pbo: 37 (24.03)</td>
<td></td>
<td>Pbo: 118 (38.44)</td>
<td>Pbo: 130 (39.88)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>Ada: 21 (13.64)</td>
<td>3 (30)</td>
<td>Ada: 33 (10.75)</td>
<td>Ada: 9 (2.76)</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Other</td>
<td>NR</td>
<td>2 (20)</td>
<td>Ada: 4 (1.3)</td>
<td>Ada: 11 (3.37)</td>
<td>15 (100)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pbo: 7 (2.28)</td>
<td>Pbo: 13 (3.98)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pbo: 96.5 (24.8)</td>
<td></td>
<td>Pbo: 99.3 (25.13)</td>
<td>Pbo: 95.7 (25.87)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI (kg/m², n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>Ada: 15 (9.74)</td>
<td></td>
<td>Ada: 24 (7.82)</td>
<td>Ada: 36 (11.04)</td>
<td>7 (46.7)</td>
<td>0</td>
<td>Ada: 32 (25.7–38.4)</td>
<td>28.4 (6)</td>
</tr>
<tr>
<td></td>
<td>Pbo: 9 (5.84)</td>
<td></td>
<td>Pbo: 13 (4.23)</td>
<td>Pbo: 26 (7.98)</td>
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</tr>
</tbody>
</table>

(continued)
Table 2. Baseline Characteristics of Participants (continued)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>Ada: 65 (42.21)</td>
<td>NR</td>
<td>Ada: 97 (31.60)</td>
<td>Ada: 85 (26.07)</td>
<td>4 (26.7)</td>
<td>8 (80)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Pbo: 36 (23.38)</td>
<td></td>
<td>Pbo: 103 (33.55)</td>
<td>Pbo: 117 (35.89)</td>
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<tr>
<td></td>
<td>Pbo: 13.4 (10.4)</td>
<td></td>
<td>Pbo: 9.4 [1.0, 43.0]</td>
<td>Pbo: 9.9 [1.2, 68.5]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Ada: 56 (36.36)</td>
<td>NR</td>
<td>Ada: 81 (52.60)</td>
<td>Ada: 105 (32.20)</td>
<td>12 (80)</td>
<td>4 (40)</td>
<td>Ada: 10 (47.62)</td>
<td>12 (70)</td>
</tr>
<tr>
<td>Hurley stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>Ada: 73 (47.40)</td>
<td>NR</td>
<td>Ada: 80 (51.95)</td>
<td>Ada: 86 (26.38)</td>
<td>9 (60)</td>
<td>2 (20)</td>
<td>NR</td>
<td>11 (55)</td>
</tr>
<tr>
<td></td>
<td>Pbo: 36 (23.38)</td>
<td></td>
<td>Pbo: 81 (52.6)</td>
<td>Pbo: 89 (27.30)</td>
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<td></td>
</tr>
<tr>
<td>III</td>
<td>Ada: 30 (19.48)</td>
<td>NR</td>
<td>Ada: 73 (47.40)</td>
<td>Ada: 77 (23.62)</td>
<td>6 (40)</td>
<td>8 (80)</td>
<td>NR</td>
<td>9 (45)</td>
</tr>
<tr>
<td></td>
<td>Pbo: 15 (9.74)</td>
<td></td>
<td>Pbo: 73 (47.40)</td>
<td>Pbo: 74 (22.70)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline pain score</td>
<td>Ada: 52.5 (25.36)</td>
<td></td>
<td>Ada: 5.1 (2.51)</td>
<td>Ada: 4.3 (2.62)</td>
<td>4.6 (0.60)</td>
<td>5.9 (2.59)</td>
<td>Ada: 58 (40.63–75.37)</td>
<td>4.8 (NR)</td>
</tr>
<tr>
<td></td>
<td>Pbo: 57.8 (28.5)</td>
<td></td>
<td>Pbo: 4.8 (2.68)</td>
<td>Pbo: 4.8 (2.73)</td>
<td></td>
<td></td>
<td>Pbo: 36.17 (5.97–66.37)</td>
<td></td>
</tr>
</tbody>
</table>

N = number of participants; f = female; m = male; SD = standard deviation; 95%CI = 95% confidence interval; NR = not reported; VAS = visual analogue scale; NRS = pain numerical rating scale; BMI = body mass index.
Methodological Quality Assessment

The methodological quality of the 4 included RCTs [14,23,24] was assessed through the Cochrane Risk of Bias tool (Figure 2). The overall risk for these studies was found to be low. The 2 open-label uncontrolled studies were assessed through the MINORS tool (Table 3) and were found to be high risk. The observational studies were assessed through the Quality assessment tool for observational cohort and cross-sectional studies and their methodological quality was deemed fair (Table 4). According to the funnel plot no publication bias was detected (Figure 3).

Outcomes

Quantitative synthesis of the 4 controlled studies was possible for the primary outcome (data available for a total of 282 patients in the intervention group and 266 patients in the control group) (Figure 4). VAS values [14,24] were converted to PGA-NRS values through dividing by 10. The

![Methodological Quality Assessment](Image)

**Figure 2.** A Overall risk of bias of randomized controlled trials, calculated with the Cochrane Risk of Bias tool. B Risk of bias of individual randomized controlled trials, calculated with the Cochrane Risk of Bias tool.
### Table 3. Methodological Index for Non-randomized Studies (MINORS)

<table>
<thead>
<tr>
<th>Assessed items</th>
<th>Amano et al 2010</th>
<th>Morita et al 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A clearly stated aim</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2. Inclusion of consecutive patients</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Prospective collection of data</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4. Endpoints appropriate to the aim of the study</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5. Unbiased assessment of the study endpoint</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6. Follow-up period appropriate to the aim of the study</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7. Loss to follow up less than 5%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8. Prospective calculation of the study size</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>9. An adequate control group</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10. Contemporary groups</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>11. Baseline equivalence of groups</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>12. Adequate statistical analyses</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td><strong>Judgement</strong></td>
<td>High risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Methodological Index for Non-randomized studies (MINORS) scale contains 8 assessment points for non-comparative studies and 4 extra points for comparative studies[19]. Each item receives 0, 1 or 2 points, if it is not reported, reported but inadequate or reported and adequate respectively, with an ideal overall score of 16 for non-comparative and 24 for comparative studies.

N/A = not applicable or not available?

### Table 4. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

<table>
<thead>
<tr>
<th>Assessed Items</th>
<th>HOPE 2019</th>
<th>Caposiena Caro et al 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the research question or objective in this paper clearly stated?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Was the study population clearly specified and defined?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Was the participation rate of eligible persons at least 50%?</td>
<td>Yes</td>
<td>Not reported</td>
</tr>
<tr>
<td>4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Was a sample size justification, power description, or variance and effect estimates provided?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)?</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10. Was the exposure(s) assessed more than once over time?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>12. Were the outcome assessors blinded to the exposure status of participants?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13. Was loss to follow-up after baseline 20% or less?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Overall rating (good, fair, poor)</strong></td>
<td>Fair</td>
<td>Fair</td>
</tr>
</tbody>
</table>
meta-analysis performed showed that adalimumab administered for 12 weeks significantly decreased pain compared to placebo (-0.418 reduction in mean pain score [95% CI -0.588, -0.248] and \( P = 0.000 \)). There was very little heterogeneity across studies based on the \( I^2 \) statistic (2.985). Only the “adalimumab every week” arm of Scheinfeld et al [14] was included in the meta-analysis, as statistical data regarding the “adalimumab every other week” arm was missing. We contacted authors via email in an effort to acquire this data, but they did not respond.

No quantitative synthesis of controlled studies was possible for the secondary outcome, due to missing data (email communication with authors was fruitless). According to Scheinfeld et al [14], 63% (\( P < 0.001 \)) and 43% of patients
receiving adalimumab every week and every other week respectively achieved minimum clinically important difference in pain at week 12 (defined as half of standard deviation of baseline pain score) comparing to 26% of patients receiving placebo [30]. The same study revealed that 52.1% (P < 0.001) and 27.7% of patients receiving adalimumab every week and every other week, respectively, achieved ≥50% reduction in baseline VAS score at week 12, contrary to 18.8% of patients receiving placebo [14]. According to PIONEER I, 27.9% of patients receiving adalimumab and 24.8% of patients receiving placebo achieved NRS30 at week 12 (P = 0.628) [23]. According to PIONEER II, 45.7% of patients receiving adalimumab and 20.7% of patients receiving placebo achieved NRS30 at week 12 (P < 0.001).

Amano et al found that the median VAS pain score decreased from 60.0 to 57.5 at week 12 (P = 0.55) [25]. Morita et al found that 66.7% (95%CI 29.9, 92.5) of participants achieved NRS30 at week 12. According to the Swedish post-marketing study, pain score decreased by 3.5 (95% CI 1.04, 5.96) after 12 weeks of adalimumab (P = 0.0147) (data available for 6 patients) [28]. Caposiena Caro et al measured a 1.3 reduction in VAS score after 12 weeks of adalimumab (no variance or significance data reported) [27].

**Conclusions**

We performed a meta-analysis of 4 good-quality RCTs assessing the efficacy of adalimumab in reducing HS-related pain. Adalimumab was found significantly superior to placebo regarding pain score reduction after 3 months of treatment. Our systematic review yielded 4 more open-label uncontrolled studies, 2 of which [26,28] showed that mean pain scores reduced significantly after 12 weeks of adalimumab treatment. In light of the severe impact of pain on HS patients’ quality of life and the established under-treatment or difficult treatment of HS-related pain, the key finding of this study suggests that dermatologists should consider adalimumab when pain is a primary concern of a HS patient (in terms of severity, frequency and/or perception).

The limitations of our study are the small number of studies included in the quantitative synthesis, which, however, reflects the actual paucity of evidence regarding the effect of adalimumab on HS-associated pain. What is more, the main body of evidence included in this review and analysis came from pre-drug-approval RCTs, which, though solid methodologically, may not accurately simulate real-life conditions eg strict inclusion and exclusion criteria, higher treatment compliance, more frequent doctor visits, etc. Another limitation of our study is that we did not check for confounding factors such as the impact of mood improvement on pain perception.

Pain is the principal determinant of life quality in HS patients [31]. A recent (2020) cross-sectional study included 1,795 HS patients, 83.6% of whom experienced pain [32]. Pain intensity correlated positively with female gender, smoking, multiple affected areas and more severe disease [32]. Commonly employed HS treatments offer inadequate pain relief and, on top of this, dermatologists tend to be insufficiently trained in clinical pain management [31]. As a result, patients frequently self-medicate and may expose themselves to the dangers of opioid or other substance misuse [31]. On another note, 82% of 110 HS patients tried to alleviate their pain through manually draining pus from their own lesions [33]. According to the European guidelines for the treatment of HS [34] a holistic approach is mandatory, when deciding how to manage HS patients. Aside from the principal pharmaceutical therapy, a plan should be made, among other things, for handling pain. There is, however,
only low-strength evidence (D) for the administration of common mild (nonsteroidal anti-inflammatory drugs) and strong (opioids) analgesics [34]. Therefore, well-studied drugs against HS with an established pain-reducing action, like adalimumab, are most precious weapons in the dermatologist’s arsenal.

Increased TNF-a levels in HS patients, and improvement of HS in patients with Crohn disease receiving adalimumab, led to adalimumab being tried as a primary treatment for moderate-to-severe HS [35]. Trials showed that the drug is both efficacious and easily tolerated, while positively affecting important secondary endpoints, like quality of life and pain [35]. Secukinumab reduced VAS pain score in a reported case of recalcitrant HS and its efficacy against HS is currently being examined in clinical trials [36]. Ustekinumab brought about significant reduction in VAS pain score in one phase II open-label trial of patients with moderate-to-severe HS [37]. Apremilast was also found to significantly reduce VAS pain score in a case-series of 9 patients (P = 0.026) [38].

It has been undoubtedly established, that pain should be brought into focus as far as HS-related research is concerned. Existing and potential new anti-HS drugs should be studied more rigorously in terms of their ability to mitigate acute and chronic HS pain, while standardized pain outcome measures, such as the newly introduced pain index, should be consistently used across such studies [39]. On the other hand, high-quality large-scale studies testing the efficacy and safety of various analgesics in HS patients should be designed and conducted soon. This evidence will act as the basis for the issuing of pain-specific treatment guidelines that will support dermatologists in their difficult role and improve the life-quality of HS patients.

References


Serological Biomarkers and Their Detection in Autoimmune Bullous Skin Diseases

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Key words: diagnostics, pemphigoid, pemphigus, antibodies

Citation: Heckler I, Hong M, Sinha A, Venkataraman I. Serological Biomarkers and Their Detection in Autoimmune Bullous Skin Diseases, Dermatol Pract Concept. 2022;12(2):e2022116. DOI: https://doi.org/10.5826/dpc.1202a116

Accepted: November 22, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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ABSTRACT

Autoimmune bullous diseases (AIBDs) are a group of skin-related disorders that involve damage to structures maintaining cell-cell adhesion, such as desmosomes and hemidesmosomes. Key AIBDs include pemphigus related diseases, pemphigoid related conditions, acquired epidermolysis bullosa (EBA), and dermatitis herpetiformis (DH). Each group of conditions exhibits characteristic clinical lesion patterns and is associated with specific autoantibodies targeting epidermal and dermal structures involved in cell-cell adhesion and skin integrity. Pemphigus diseases primarily target desmoglein (Dsg) 3 and Dsg1 proteins but several non-Dsg autoantibodies have also been linked to pemphigus. Pemphigoid diseases typically target bullous pemphigoid (BP)180 and BP230; EBA is associated with antibodies directed against anti-type VII collagen and DH by IgA autoantibodies against tissue transglutaminase and deaminated gliadin. Investigation into the serological biomarkers found in AIBDs have allowed the development of diagnostic assessments (i.e. tissue antibody detection and serological testing) based on the unique autoantibody profiles of a particular disease group. The methods for the detection and quantification of disease-associated autoantibodies continue to evolve and improve.

Introduction

The skin is the largest organ of the body, protecting us from the environment, regulating body temperature and permitting the sensation of touch. It is divided into 3 main layers: the outermost epidermis layer, the middle dermis layer and the lower hypodermis layer [1]. The epidermis is mainly made up of keratin producing cells called keratinocytes. The protective barrier, regulation of epidermal temperature and nutrients and other functions of the epidermis are dependent upon the maintenance of stable connections between keratinocytes and other epidermal structures primarily mediated by adhesive desmosomal and hemidesmosomal proteins [2]. Desmosomes are specialized tight junctions critical to cellular adhesion (Figure 1). They are arranged on adjacent sides of plasma membranes and can be seen in tissues
including cardiac muscle, gastrointestinal mucosa, and epithelia, all of which can be subject to significant mechanical stress during normal physiological and disease states [3].

Within desmosomes, there is a vast network of cadherin proteins (desmogleins, desmocollins and desmoplakins), linker proteins (e.g., plakoglobin, plakophilin) and keratin intermediate filaments, that connect as desmosome-intermediate filament complexes (DIFCs). Desmoplakin, which coordinates other cadherin proteins and keratin filaments, is the most prevalent protein within the desmosome [4].

Hemidesmosomes resemble tiny stud-shaped structures and are similar in shape to desmosomes. However, there are several differences between these 2 structural components. Hemidesmosomes attach keratinocytes to the extracellular matrix and utilize integrins rather than desmogleins and desmocollins. Key hemidesmosomal-associated proteins include the cytoplasmic protein BP230, the transmembrane protein BP180, laminin 332 and collagen type VII [5]. Another feature of hemidesmosomes is their role in signaling pathways, relevant for the migration of keratinocytes (Figure 1) [6].

Autoimmunity involves the presence of antibodies (produced by B lymphocytes) and T lymphocytes that have escaped mechanisms of self-tolerance, both centrally and peripherally, that are reactive to one’s own self-antigens. When auto-reactive lymphocytes cause enough target tissue damage, autoimmune disease can occur.

There are over 80 human autoimmune diseases in existence, affecting over 20 million Americans [7]. Indicators of autoimmunity (i.e., antinuclear antibodies) suggest that the incidence of autoimmune disease has been increasing over the past few decades [8].

Collectively, autoimmune diseases present a tremendous, and likely under-estimated burden on healthcare costs: over $100 billion annually in the United States [9]. These costs...
reflect a multitude of factors which are impacted by delays in diagnosis, poor or infrequent monitoring of disease activity leading to less than optimal disease management.

Systemic autoimmune diseases affect multiple organs, whereas organ-specific diseases target a single organ such as the skin. Autoimmune diseases that affect the skin include vitiligo, scleroderma, lupus, psoriasis, vasculitis, and autoimmune bullous dermatoses (AIBDs). AIBDs are a collection of autoimmune skin specific disease characterized by the production of autoantibodies against structural components of the skin including desmosomes and hemidesmosomes [10]. Such an autoimmune reaction interferes with intercellular connections within the epidermis in addition to the crucial linkage between the epidermis and the dermis. AIBDs manifest as skin layer separation and blistering and are divided into 4 main groups according to their target antigens and localization of the blisters: pemphigus diseases, pemphigoid diseases, acquired epidermolysis bullosa (EBA), and dermatitis herpetiformis (DH) (Table 1) [10].

Clearly, there is need for a greater understanding of the epidemiology, pathophysiology, and natural history of AIBD. The continued evolution of methods for the reliable, accessible, and cost-effective detection of disease relevant autoantibodies is an ongoing endeavor to improve our ability to diagnose and monitor autoimmune activity, with impact in clinical management and decision-making accurately and rapidly.

### Objectives

Here, we discuss the key autoantigens in AIBDs and highlight how serological testing can be used in conjunction with clinical symptoms for diagnostic purposes.

### Pemphigus diseases

Pemphigus diseases are commonly characterized by the production of autoantibodies primarily against the desmosomal proteins desmoglein (Dsg)3 and Dsg1 which results in the loss of epidermal cell-cell adhesion and subsequent blister formation [11]. Some patients experience only mucosal membrane erosions with minimal skin blistering, others exhibit lesions on both mucosal as well as non-mucosal surfaces, while others still may only show skin involvement without mucous membrane involvement [11]. The clinical phenotype of pemphigus has been linked to defined Dsg3 and Dsg1 antibody profiles [12]. Additionally, differences in the normal tissue distribution of Dsg1 and Dsg3 proteins (Dsg1 on the epidermal surface and Dsg3 in deep epidermal layers/mucous membranes) may explain the varying clinical manifestations of different pemphigus forms [13]. For example, in pemphigus foliaceus (PF), IgG antibodies are only directed against Dsg1 and blistering is confined to the skin surface. On the other hand, in pemphigus vulgaris (PV), autoantibodies against both Dsg1 and Dsg3 can be observed, and

| Table 1. Target antigens in autoimmune bullous dermatoses |
|---------------------------------|------------------|-----------------|-----------------|
| **AIBD Subtype** | **Blister Location** | **Target Antigena** | **Ig Type** |
| PV (mucosal-dominant type) | Intraepidermal | Dsg3 | IgG |
| PV (mucocutaneous type) | Intraepidermal | Dsg3, Dsg1, Dsc1, Dsc2, Dsc3 | IgG |
| IgA Pemphigus | Intraepidermal | Dsg3, Dsg1, desmocollins | IgG |
| PF | Intraepidermal | Dsg1 | IgG |
| PNP | Intraepidermal | Envolakin, Dsg3, Dsg1, periakin, epilakin, plectin, desmoplakins, Dsc(1-3), BP230, α2-macroglobulin-like 1 | IgG |
| **Pemphigoid** | | | |
| BP | Subepidermal | BP180, BP230 | IgG |
| MMP | Subepidermal | BP180, BP230, laminin332, integrin α6/β4, and collagen VII | IgG |
| EBA | Subepidermal | Type VII collagen | IgG |
| DH | Subepidermal | Epidermal/tissue transglutaminase, endomysium, deamidated gliadin | IgA/IgG |
| Pemphigoid gestationis | Subepidermal | BP180, BP230 | IgG |
| Linear IgA bullous dermatosis | Subepidermal | Ectodomain fragment of BP180, BP230 | IgA |

aMain target antigens are indicated in bold.

AIBD = autoimmune bullous dermatoses; PV = pemphigus vulgaris; PF = pemphigus foliaceus; Dsc = desmocollins; PNP = paraneoplastic pemphigus; BP = bullous pemphigoid; MMP = mucous membrane pemphigoid; EBA = epidermolysis bullosa acquisita; DH = dermatitis herpetiformis; Dsg = desmoglein.
the degree of blistering and mucous membrane involvement varies based on the prevalence of either anti-Dsg1 and anti-Dsg3 [12]. This framework, correlating the clinical presentation of pemphigus to antibody profile, is known as the Dsg compensation hypothesis (DCH), featured prominently in dermatology textbooks and previous research studies [14].

As elegant as the hypothesis may be, however, recent studies have identified exceptions to this hypothesis [15,16]. PV accounts for 80% of all pemphigus cases and mainly affects middle-aged and elderly populations [17]. While Dsg3 (89% - 90% of patients) and Dsg1 (50% - 60% of patients) are the major autoantigens in PV, additional structural and metabolic autoantigens have been identified including desmocollins (Dsc) 1 and 3, mucaric and nicotinic acetylcholine receptors, mitochondrial antigens, thyroid peroxidase, hSPCA1, plakophilin 3, plakoglobin, and E-cadherin [18]. Studies have shown that autoantibodies against these additional targets may complement the effects of anti-Dsg autoantibodies and explain individual variations in pemphigus disease severity [18].

In paraneoplastic pemphigus (PNP), autoantibodies are directed against desmosomes including Dsg1 and Dsg3, α2-macroglobulin-like 1, and the plakins envoplakin, desmoplakin I and II, plectin, periplakin and the hemidesmosome BP230. The presence of desmoplakin autoantibodies is also common to PV, PE, and BP. However, autoantibodies for envoplakin and periplakin on immunoblot, as well as autoantibodies for desmoplakin (on indirect immunofluorescence and rat bladder epithelium), appear to be sensitive and specific for PNP diagnosis [19]. This has led to the development of an enzyme-linked immunosorbent assay (ELISA) that detects envoplakin in consideration for a diagnostic tool for PNP.

PNP is associated in a majority of cases with non-Hodgkin lymphoma, chronic lymphocytic leukemia and Castleman disease [20]. A common clinical feature is stomatitis which presents with painful erosions and ulcerations of the oropharynx. Anti-envoplakin antibodies are highly specific for PNP and are used for the differentiation of PNP from other AIBDs [21].

In IgA pemphigus, a rare form of pemphigus with unclear etiology, serum IgA autoantibodies are associated with reactivity against the desmosomal cadherins Dsc1, Dsc2, Dsc3, Dsg1, and Dsg3 [17]. These circulating IgA antibodies lead to formation of pruritic and painful eruptions that present as vesicles and pustules on the skin [22]. As IgA pemphigus is so rare, there is currently no reported sex, age, or race distribution of this disease. However, IgA pemphigus has been observed in all age demographics [23].

**Pemphigoid diseases**

Pemphigoid diseases are characterized by subepidermal blister formation in the skin and mucous membranes [24]. Pemphigoid diseases occur when the immune system produces autoantibodies against proteins involved in the linkage between the epidermis and dermis. As a result of this autoimmune reaction, the epidermal layer separates from the dermis. Several different types of pemphigoid diseases exist including bullous pemphigoid (BP), pemphigoid gestationis, mucous membrane pemphigoid, linear IgA dermatosis and p200 pemphigoid [10].

The hemidesmosomal proteins, BP180 and BP230, which tether the 2 skin layers together, are the common autoantibody targets in BP. BP is the most common AIBD in the general population, with an annual incidence ranging between 2.3 to 23 cases per million. BP disproportionately affects elderly people, with an incidence of 190-312 cases per million among those 80 years and older [14]. This disease manifests with bulging skin blisters and minimal mucous membrane involvement [25]. Unlike pemphigus, BP shows a negative Nikolsky sign (ie no splitting of skin upon applying pressure) [26].

Autoantibodies against BP180 represent the most significant biomarker in BP due to their high prevalence [27]. Additional screening for anti-BP230 antibodies is important as they occur in 40% of patients who are seronegative for anti-BP180 antibodies. The parallel detection of both anti-BP230 antibodies and anti-BP180 antibodies increases the sensitivity of BP detection significantly, to a combined 97.1% [28]. Pemphigoid gestationis is the manifestation of BP in pregnant women and is characterized by autoantibodies predominately against epitopes in the immunodominant NC16A domain of BP180 (BP180-NC16A) [29]. In children, linear IgA dermatosis occurs from the autoantibody recognition of the ectodomain fragment of BP180 [30]. In addition to BP180, laminin 332 is a major target in mucous membrane pemphigoid (MMP) [31]. Additionally, patients with mucous membrane pemphigoid may show antibodies against BP230, integrin α6β4, and collagen VII [31,32]. The identification of anti-laminin 332 is important for determining a patients prognosis as anti-laminin 332 positive patients seem to be at an increased risk of malignancies [33].

**Epidermolysis bullosa acquisita**

EBA is a severe blistering dermatosis characterized by autoantibodies against type VII collagen [34]. EBA manifests as subepidermal blisters and erosions in response to the minor irritation of skin and affects both the skin and mucous membranes. The level of the cleavage in the basal membrane contributes to the various phenotypes of EBA, including the most common inflammatory and mechanobullous (noninflammatory) variants [35].

**Dermatitis herpetiformis**

DH is an itchy dermatosis affecting 10% of celiac patients. It manifests as blisters in the subepidermis of areas such as the
elbows, knees, and buttocks. There is also minimal blistering of the mucous membranes. DH is one of many manifestations of gluten-sensitivity and is characterized by IgA autoantibodies against endomysium tissue/epidermal transglutaminase (anti-tTG/-eTG) and/or deamidated gliadin (IgA/IgG) [36]. In contrast to the increase in diagnosis of celiac disease, DH incidence appears to be decreasing (Table 1) [37].

Diagnostic approach

The diagnosis of AIBDs requires the detection of both circulating and tissue-bound antibodies, and histopathology, in conjunction with clinical symptoms [38]. The pathway to AIBD diagnosis can be broken down into 4 pillars. First, the clinical manifestations of the disease must be assessed. Second, histopathology can be performed to provide information on the location of skin involvement (sub- or intraepidermal separation). Third, the detection of tissue bound autoantibodies by direct immunofluorescence (DIF) is done. DIF is the current diagnostic gold standard for AIBDs but gives limited information on the target antigens. DIF has a sensitivity of 82% - 91% and a specificity of 98% [17]. The fourth pillar is the identification of autoantibodies by serological testing such as indirect immunofluorescence (IF) microscopy, monospecific ELISA or immunoblot techniques [17].

Serological testing for the detection of circulating antibodies in AIBDs has the advantage of being minimally invasive and may be suitable for diagnostic purposes in conjunction with the clinical manifestations, and for aiding therapy decisions and disease prognosis [17]. Conventional serological detection of AIBD-specific antibodies involves an initial IIF screen using tissue substrates, followed by an antigen-specific assay such as ELISA.

In 2016, the International Bullous Diseases Consensus Group met to standardize the diagnosis and management of pemphigus [39]. The diagnosis of pemphigus was agreed to be based on the clinical presentation and histopathology consistent with pemphigus and either a positive DIF microscopy or serologic detection of autoantibodies against epithelial cell surface antigens [39]. The determination of serum autoantibodies was recommended for therapeutic decision making as serum levels of IgG against Dsg1 and Dsg3 correlate with the clinical activity of pemphigus.

AIBD autoantibody screening using tissue IIF

Due to their high sensitivity, tissue substrates are ideal for screening for AIBDs autoantibodies (esophagus, salt-split skin, bladder mucosa) [40]. The esophagus substrate yields characteristic honeycomb-like immunofluorescence patterns which can be differentiated when screening for antibodies in suspected cases of PV or PF. IIF using esophagus as a substrate has proven to be useful for the detection of autoantibodies against Dsg1 and Dsg3, with a sensitivity of 81% - 100% and a specificity of 89% - 100% [17,41]. For the differentiation of autoantibodies in subepidermal AIBDs, tissue sections of salt-split skin are used [42]. Salt-split skin substrate has a sensitivity of 73% - 96% and a specificity of 97% for such subepidermal antibodies. Additionally, as antibodies have varying antigenic binding properties on salt-split skin, this allows for the differentiation between the subepidermal AIBDs BP, pemphigoid gestationis, linear IgA dermatosis and other subepidermal AIBDs such as EBA, and anti-laminin-332-type MMP. Where BP180 and BP230 are located on the epidermal side of salt-split skin, collagen type VII and laminin 332 remain on the dermal side.

Urinary bladder is an ideal substrate for distinguishing between PNP and other pemphigus diseases as plakins like envoplakin are highly expressed in the bladder while Dsg1 and Dsg3 are not [43]. Urinary bladder is therefore a highly specific substrate for PNP (99% - 100%) and having a sensitivity of 74% [17]. Finally, liver tissue is useful for the detection of IgA autoantibodies against endomysium in DH [44].

The International Bullous Diseases Consensus Group recommends using IIF microscopy on monkey esophagus or human skin to detect autoantibodies against surface proteins of epidermal keratinocytes [39]. In cases of atypical presentation or the suspicion of another AIBD, the use of IIF microscopy on rat bladder and immunoblot/immunoprecipitation is discussed. They also describe the use of recombinantly expressed Dsg1, Dsg3, or envoplakin substrates (EUROIMMUN) when Dsg- or envoplakin-specific ELISA cannot be used [39].

Antigen-specific detection of AIBDs

The detection of antigen-specific autoantibodies in AIBDs can be achieved using monospecific IIF and ELISAs [17]. Monospecific IIF can be accomplished using transfected cells as a substrate in which the target antigen has been recombinantly expressed. Additionally, designer antigens have been created to enhance diagnostic sensitivity and specificity of IIF. Such purified recombinant designer antigens are utilized as monospecific IIF substrates. BIOCHIPS, which are coated with an IIF substrate and arranged onto microscope slides, allow for autoantibody screening and confirmatory discrimination in a single incubation. In this way, various types of AIBDs can be screened for in one test. IIF BIOCHIP mosaics contain combinations of different substrates (esophagus, salt-split skin, bladder mucosa, transfected cells, purified designer antigens). A study which compared the performance of the “Dermatology Mosaic 7” with a multiparametric BIOCHIP mosaics offer a cost and time effective IIF method.
Autoantibodies can be mono-specifically identified using ELISAs which utilize purified recombinant proteins [17]. Commercial assays which utilize the recombinant ectodomains of Dsg1 and Dsg3 have a high sensitivity and specificity for the detection of pemphigus foliaceus and pemphigus vulgaris (96% - 100%, 96% - 100% and 85% - 100%, 96 - 100%, respectively) [17]. In addition to their use as monospecific substrates in IIF, designer antigens have been developed for ELISAs (for the detection of antibodies against BP180 and BP230, deamidated gliadin peptides) to improve immunoreactivity. ELISA techniques provide quantitative measurement which is useful for the application of therapy monitoring. Profile ELISAs containing a combination of antigens enables the simultaneous detection of multiple AIBDs subtypes in patients with suspected AIBDs.

Experts recommend determining anti-Dsg1 and/or anti-Dsg3 IgG antibodies by ELISA for the detection of PF, and mucosal/mucocutaneous PV (Mannose-Binding Lectin, EUROMMUN) [39]. Serum concentrations of antibodies against Dsg1 and Dsg3 are associated with pemphigus disease activity in and high levels of anti-Dsg1 by ELISA has a positive predictive value for skin relapses. Therefore, the determination of serum autoantibodies against skin structural proteins by ELISA has a prognostic value for guiding pemphigus treatment.

Conclusions

A definitive diagnosis of AIBD is based on a combination of clinical signs and symptoms and the analysis of autoantibodies using IIF and ELISA. IIF, using various tissue substrates, is a useful application for antibody screening while transfected cells and purified antigen substrates are suitable for antigen-specific IIF. ELISA allows for the quantitative measurement of antibody levels to support the detection of different AIBD subtypes. Serological antibody testing is important for distinguishing between the various AIBD subtypes due to differences in their prognosis and treatment.

Immunologic testing has also a key role in providing an accurate diagnosis as blistering skin diseases are easily misdiagnosed. Oral blisters are often misdiagnosed as an infection such as candidiasis or herpes. Without a proper diagnosis, a patient is at risk of being mistreated, potentially with a chronic overexposure to steroids which may reduce some symptoms without fully addressing the underlying problem.

Additionally, serological testing allows for the monitoring of AIBD disease. Serum levels of anti-BP180 antibodies correlate with disease activity of BP while anti-BP230 levels correlate with the disease duration [43]. Moreover, levels of anti-Dsg1 and Dsg3 are associated with severity of pemphigus diseases and response to therapy while anti-ennoplakin titers correlate with the degree of PNP symptoms as well as differential diagnostic clarification [46]. The detection of anti-collagen type VII antibodies aids in the detection of EBA and allows for the differentiation of EBA from other AIBDs [47,48]. In addition to disease monitoring, correlations between lowered levels of AIBDs specific autoantibodies in response to therapy point to the use of serological testing for therapy monitoring purposes [49,50].

Continued efforts to develop and deploy increasingly accurate and multi-parameter methods for the detection of the comprehensive set of AIBD-associated autoantibodies can be expected to enhance diagnostic efforts and further our understanding of disease mechanisms, progression and response to therapy.

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Neck Rejuvenation With a New Infrared Emission

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Key words: ipl, facial aging, infrared emission, wrinkles


Accepted: August 2, 2021; Published: April, 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Human skin aging includes histological and biochemical changes. The therapeutic technology of non-invasive skin rejuvenation of Intense Pulsed Light (IPL) is called photorejuvenation, and the technique has been used widely in cosmetic dermatology to improve facial photoaging. IPL sources are multiwavelength lights that typically emit light in the 500 to 1200 nm range. At this level, the thermal impulse causes denaturation of collagen fibers with consequent formation of new ones [1]. Papers that elucidate how systems emitting light near-infrared (800–1200 nm) could produce, on human skin fibroblasts cell cultures, dermal changes in gene expression and extracellular matrix and contribute to photorejuvenation are already present in literature [2].

Case Presentation

We present our preliminary experience with a 63-year-old female patient treated with a new pulsed infrared emission in the range 800–1200 nm (Luxea, Deka Mela Srl). Four sessions spaced 2 weeks apart were performed. The patient was recruited at Magna Graecia University of Catanzaro and signed informed consent. Local ethical committee approved the treatment protocol. The patient was photographed at the beginning and 3 months after the last treatment session (Figure 1).

The system is based on the pulsed emission of a wavelength range of 800–1200 nm over a 6.2 cm² spot. The protocol used the following settings: power 30 W, handpiece moving in a linear slow motion creating an area about 5 × 5 cm. The handpiece is kept in a vertical position and in contact with the skin by applying light pressure and transparent water gel so that the entire surface of the irradiation area is always in contact with the skin. The protocol provides a progressive skin temperature rise of the epidermis up to 40-42 °C, persisting, as long as conditions allow, for a few minutes on the treatment area. The patient achieved an improvement in skin texture. A better skin tone and wrinkle reduction were observed in the neck area.
Patient in the immediate post-treatment experienced an improvement in brightness and porosity of the skin. The immediate effects are visibly enhanced 2 months after the first treatment session. The response of the dermal tissue is noticeable within 5 minutes. The endpoint was considered light erythema associated with the sensation of heat reported by the patient that disappeared in 30 minutes.

Conclusions

Light devices emitting near-infrared are highly effective for skin rejuvenation. These treatments are associated with minimal patient discomfort and are well tolerated. In this context, patients require increasingly effective treatments associated with minimal pain and with the lowest possible risk of side effects. The new pulsed infrared emission in the range 800–1200 nm could be an excellent non-invasive system. Furthermore, this emission mode is convenient in the neck area where the alternatives are few and still invasive. The strength of this treatment is the absence of downtime and side effects. These results promise a rapid spread of this technology and are the starting point for combined treatments to treat more complex diseases that require integrated approaches.

References

Ribociclib-induced Vitiligo: a Case Report

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Key words: vitiligo, ribociclib, selective cyclin-dependent kinase 4/6 inhibitors, breast cancer, adverse event


Accepted: July 29, 2021; Published: April, 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Selective cyclin-dependent kinase 4/6 inhibitors (CDK 4/6i) – ribociclib, palbociclib and abemaciclib – are a novel therapeutic option for breast cancer [1]. CDK 4/6is are well tolerated and have shown a manageable safety profile, with mild hematological, gastrointestinal and cutaneous adverse events (AE). Vitiligo-like lesions are a dermatologic AE exceptionally reported with CDK 4/6is use [2].

Case Presentation

A 70-year-old woman presented with a 6-week history of asymptomatic facial hypopigmented spots. For the last 8 months, she was receiving treatment with letrozole and ribociclib for a hormone receptor-positive (HR-positive) and human epidermal growth factor receptor-2-negative (HER2-negative) metastatic breast cancer. Dermatological examination revealed unpigmented, well-defined macules distributed symmetrically in the neck and the face, with affectation of hair follicle (Figure 1, A and B). The Wood lamp examination showed bright white and sharply delineated lesions (Figure 2). Based on these findings, a diagnosis of vitiligo was made.

Discussion

Vitiligo is an acquired pigmentary autoimmune disorder consisting of the development of hypopigmented macules due to the selective loss of melanocytes. The cause of vitiligo remains unknown. Vitiligo-like lesions have been reported as an AE in oncological patients treated with anti-programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) immunotherapies (pembrolizumab, nivolumab), as well as in patients treated with tyrosine-kinase inhibitors (imatinib, cabozantinib, pazopanib) [2]. It is considered an indicator of survival benefit in melanoma patients treated with anti-PD-1/PD-L1 immunotherapies.

Selective CDK 4/6is are currently approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer. Hematologic toxicity, gastrointestinal disturbances and fatigue are the most frequent side effects of this class of agents [1]. The most common dermatological adverse event is alopecia, which might be increased by the association of endocrine therapy. Moreover, pruritus and a maculopapular rash have also been reported as cutaneous adverse reactions in patients treated with ribociclib [1,2].
Vitiligo-like lesions have been described in patients treated with CDK 4/6is too, mostly in relation to ribociclib [2]. Although the pathogenic mechanism between CDK 4/6is and vitiligo is still unclear, it has been classified as a class-related AE. The cell-cycle arrest and consequent apoptosis induced by CDK 4/6is [1], may lead to a premature death of melanocytes, that clinically manifests as achromic lesions. The prognostic meaning of vitiligo lesions in patients treated with CDK 4/6is remains still unclear.

Treatment of vitiligo induced by CDK 4/6i is challenging. Similar therapeutic strategies followed in other vitiligo patients can be performed. However, immunosuppressants and biological therapies should be avoided in oncological patients. Partial response has been achieved with topical immunosuppressants in combination with oral corticosteroids [2].

Conclusions
Depigmentation may cause psychological distress and may decreased quality of life. Therefore, oncological patients treated with CDK 4/6is should be informed about this potential AE and should be referred to a dermatologist for accurate diagnosis and treatment.

References
Introduction

The deep penetrating nevus (DPN) is a benign, acquired, melanocytic lesion that shows intense pigmentation and infiltration into the reticular dermis or subcutaneous tissue [1,2]. It affects young individuals before the third decade of life, primarily in the head and neck region. DPN usually presents as an asymptomatic, well-defined, symmetric, solitary, blue, brown, or black, papule or nodule. Due to its clinical and histopathological similarities, DPN is often confused with malignant melanoma, blue nevus, and Spitz nevus. Since dermoscopic images of DPN are scarce, its features are not well established. Here, we present a case of DPN in a patient with Fitzpatrick type V skin that showed the rainbow pattern under polarized immersion dermoscopy.

Case Presentation

A 13-year-old male with Fitzpatrick type V skin presented with a 1-year history of an enlarging lesion on the scalp. On examination, there was an 8 x 5 x 5 mm, well-defined, black, hyperkeratotic nodule with a central erosion (Figure 1A). Polarized dermoscopy with ultrasound gel immersion showed a pigmented center surrounded by rainbow patterns and bluish-white structureless areas (Figure 1B). An excisional biopsy with a 3-mm margin was performed. On histopathology, a benign-appearing, symmetric tumor composed of epithelioid and spindle-shaped melanocytes extending to the hypodermis was observed (Figure 2), compatible with DPN. At the 24-month follow-up there was no recurrence.

Conclusions

There are less than 5 dermoscopic descriptions of DPN, including a globular blue-brown pattern and a polychromatic appearance [1,2]. Polarized immersion dermoscopy is a suitable technique to evaluate nodular, melanocytic lesions, especially when hyperkeratosis, fissures, and ridges are present. The rainbow pattern and the clinical appearance of DPN in high Fitzpatrick skin types are rare findings among the
available images from the literature. Increasing awareness of this condition in skin of color, as well as selecting an adequate dermoscopy technique can help to refine the characterization of DPN in underrepresented populations.

References


Dermoscopic and Reflectance Confocal Microscopy Features of Superficial Morphea on Preexisting Atrophoderma of Pasini and Pierini

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Key words: morphea, atrophoderma, hyperpigmentation, hypopigmentation, dermatology

Citation: Song CX, Zhang YT, Tan C. Dermoscopic and reflectance confocal microscopy features of superficial morphea on preexisting atrophoderma of Pasini and Pierini. Dermatol Pract Concept. 2022;12(2):e2022048. DOI: https://doi.org/10.5826/dpc.1202a048

Accepted: July 28, 2021; Published: April, 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Superficial morphea (SM) is a distinct new variant of localized scleroderma with the collagen proliferated and deposited in the papillary and upper reticular dermis [1]. We present a case of SM developed on a primary lesion of atrophoderma of Pasini and Pierini (APP), and describe related dermoscopic and reflectance confocal microscopy (RCM) features.

Case Presentation

A 26-year-old Chinese woman presented with a seven-year-history of large hyperpigmented patches on the right leg. On examination, larger hyperpigmented patches were distributed in a zosteriform pattern. It spread from the right groin area, down the medial portions of the thigh, and finally to the popliteal fossa region. Furthermore, multiple 2 to 3 mm depigmented macules were disseminated within these hyperpigmented patches (Figure 1). Dermoscopic examination of the white spots showed whitish fibrotic beams.
and linear arborizing vessels. The pigment network was irregularly distributed with a storiform pattern in some speckled hypopigmented macules. Histological examination of a hypopigmented macule displayed decreased epidermal thickness with flattened rete pegs. There were mild superficial perivascular lymphocytic infiltrate and pronounced dense clumping and homogenization of collagen bundles, compared to the neighboring area's unaltered collagen. Discrete, highly-reflective clouds were in the “coffee-bean” pattern under RCM, which might be corresponding to the clumps of collagen in histopathology (Figure 2). These findings were consistent with the diagnosis of SM (over APP), and the application of 1% pimecrolimus ointment for 4 months showed no improvement.

Discussion

SM is typically presented with symmetric hypopigmented to hyperpigmented patches at intertriginous sites. Histologically, there are flattened rete ridges. The collagen fibers in the upper reticular dermis become thickened or homogenized, with the deeper dermis's invariable sparing. Perivascular lymphocytic infiltration is present in the superficial dermis with occasional plasma cells [2]. Dermoscopic examination of the white spots in our patient showed whitish fibrotic beams and linear arborizing vessels. The pigment network is irregularly distributed with a storiform pattern in some speckled hypopigmented macules. RCM mosaic shows marked hyperreflective areas with decreased appendageal structures.

Divergent opinions about the relationship between SM and APP are present in literature. Some authors believe that SM is not identical to APP considering the clinical depression of “cliff sign” and older age of onset in APP. SM differs itself from APP with thickened collagen in upper reticular dermis. Others believe SM and APP belong to the same entity mainly considering both share a chronic benign course and a favorable prognosis that usually needs no treatment [3,4]. Besides, APP and SM may coexist as separate entities in the same patient or association with classical morphea or systemic scleroderma, and therefore APP can be considered an abortive type of scleroderma without sclerosis [4].

Figure 2. Dermoscopic examination of the white spots showed whitish fibrotic beams and linear arborizing vessels (green arrows). (A,B) The pigment network is irregularly distributed with a storiform pattern (red oval circles) in some speckled hypopigmented macule (blue oval circles). (C) RCM mosaic shows marked hyperreflective areas with decreased appendageal structures. Histological examination of this hypopigmented macule displayed decreased epidermal thickness with flattened rete pegs. (D) Mild superficial perivascular lymphocytic infiltrate and pronounced dense clumping and homogenization of collagen bundles, compared to the neighboring area’s unaltered collagen. (E,F) Discrete, highly reflective clouds in the “coffee-bean” pattern under RCM, which might be corresponding to the clumps of collagen under the microscope.
Conclusions

The presence of discrete hypopigmented macules of SM within the primary lesion of APP adds another evidence that SM and APP are part of the same spectrum of disease. The marked hyperreflective areas with discrete, highly reflective clumped as white coffee beans. Dermoscopy and RCM can be applied as an ancillary diagnostic technique in SM.

References

Tildrakizumab: Successful Response in Two Patients With Psoriatic Arthritis

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Key words: Psoriatic arthritis, psoriasis, tildrakizumab, treatment


Accepted: July 22, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated, inflammatory arthropathy that develops in up to 30% of patients with psoriasis. Different phenotypes are recognized according to the joints involved: distal interphalangeal predominant, asymmetric oligoarticular, symmetric polyarthritis, spondylitis and arthritis mutilans. The treatment of PsA includes different therapeutic strategies: conventional disease modifying antirheumatic drugs (DMARDs) and biologic therapies such as tumor necrosis factor (TNF) inhibitors, interleukins-17 (IL-17) inhibitors, IL-12/23 inhibitor. However not all agents used for psoriasis are yet approved for PsA including IL-23 inhibitors: there are several cases of PsA successfully treated with IL-23 inhibitors.

Case Presentation

We report 2 cases of patients with PsA and psoriasis (Table 1) who successfully responded to tildrakizumab, an anti-IL-23 antibody approved only for psoriasis.

In the first case a 45-year-old man came to our unit with a 10 years history of PsA and psoriasis. The patient presented several episodes of dactylitis with radiologically documented damage to the distal interphalangeal joints. He had been treated with methotrexate (20 mg/week) for 9 months, suspended for a significant increase in transaminases (ALT 110 U/L, AST 121 U/L). We started treatment with secukinumab (300 mg sc monthly) from October 2018 to November 2019 with a partial improvement of PsA and skin disease, but the patient developed upper respiratory tract infection and the drug was stopped. Thus, the patient received tildrakizumab at the same dosage regimen as in psoriasis (100 mg sc every 12 weeks) with improvement in both diseases.

In the second case a 56-year-old woman came to our unit with a 15 years history of PsA and psoriasis. The patient suffered from peripheral asymmetric oligoarticular arthritis associated with bilateral uveitis, treated periodically with methotrexate (15 mg/week) interrupted because of several relapses. From October 2019 to September 2020, she began therapy with adalimumab (40 mg sc every 2 weeks), then stopped for the appearance of itching and skin rash. Given
the impossibility of carrying out therapy with IL-17 inhibitors due to a suspected concomitant ulcerative colitis, we started therapy with tildrakizumab from December 2020, getting a control of PsA.

**Conclusions**

IL-23/IL-17 cytokines are important players in the pathogenesis of PsA. In particular, IL-23 stabilizes the Th17 phenotype, supporting secretion of IL-17 which mediate the epidermal hyperplasia and keratinocyte differentiation. Moreover IL-23 activates the production of LTB4, exacerbating the synovial inflammation, and induces osteoclast differentiation with bone resorption result [1].

We have demonstrated that tildrakizumab is a valid therapeutic option in patients suffering from PsA, as it acts inhibiting the IL-23/IL-17 axis, the signaling pathway primarily dysregulated in this condition. It has never been described cases of patients with PsA and concomitant psoriasis with favorable response to tildrakizumab. Recent studies have been published on the approval of guselkumab in PsA [2]: considering that IL-23 is the same target, also tildrakizumab could be a useful therapeutic option for this affection.

Further studies are required to evaluate the efficacy and safety of tildrakizumab in larger cohorts of patients to consider this IL-23 inhibitor as a new promising treatment option for PsA.

**References**


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<tr>
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<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age, years</td>
<td>45</td>
<td>56</td>
</tr>
<tr>
<td>Psoriatic arthritis phenotype</td>
<td>Distal interphalangeal joints</td>
<td>Asymmetric oligoarticular joints</td>
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<tr>
<td>Systemic involvement</td>
<td>Psoriasis</td>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
<td>Uveitis</td>
<td>Uveitis</td>
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<tr>
<td>Treatment before tildrakizumab</td>
<td>Methotrexate Secukinumab</td>
<td>Methotrexate Adalimumab</td>
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Dermatology Practical & Conceptual

Spitz Nevus of the Vulva: a Very Rare Presentation of the Genital Region

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Key words: Spitz nevus, vulva, dermoscopy, melanoma

Citation: Vaccaro M, Coppola M, Lentini M, Borgia F, Moscarella E, Argenziano G. Spitz nevus of the vulva: a very rare presentation of the genital region. Dermatol Pract Concept. 2022;12(2):e2022050. DOI: https://doi.org/10.5826/dpc.1202a50

Accepted: August 8, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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Introduction

Spitz nevi of special sites, such as the vulva, appear rare and can pose a challenge as they may display worrisome clinical-dermoscopic or histopathological features [1-4]. Here we clinically, dermoscopically and histopathologically describe an extremely rare case of Spitz nevus occurring on the vulva of a 47-year-old woman.

Case Presentation

A healthy 47-year-old Italian woman presented with a 2-month history of a rapidly growing lesion on the outer surface of the left labium majus of the genitalia, without pain, pruritus or hemorrhage. Physical examination showed an asymmetric, dark-brown papule, 9 mm in diameter, well circumscribed (Figure 1A). No inguinal lymphadenopathy was revealed. Dermoscopy showed an asymmetric melanocytic lesion with a basically cobbledstone pattern, a diffuse blackish pigmentation with grayish shades and large brown-black globules, widely spaced and arranged asymmetrically (Figure 1B). An excision biopsy was made, and histological examination revealed a compound Spitz nevus, characterized by a proliferation of pigmented and epithelioid melanocytes, with no mitoses or atypical features, arranged in dermal nests and partially aligned at the dermo-epidermal junction. Melanocytes showed vesicular nuclei, small nucleoli and a homogeneous cytoplasm with many melanin granules. Mild perilesional lymphocytic infiltration was observed (Figure 2, A_C). Given the peculiar area, recent onset, rapid growth and dermoscopic features, the lesion was completely removed with clear surgical margins, and no recurrence was observed in the 6 months after the excision.

Discussion

Melanocytic lesions of the female genital area are estimated to occur in 10% to 12% of women and arise mainly in the vulva. These lesions, commonly detected during routine
dermatologic or gynecologic examination, include melanocytic nevi, melanosis, Spitz nevi, atypical melanocytic nevi of the genital type, dysplastic nevi and melanomas [4]. Spitz nevi of the vulva are very rare, with only a few cases described in the literature. Polat et al. described a case of an 11-year-old girl with a Spitz nevus on the inner surface of the labium majus of the genitalia [5]. In another retrospective study about the clinical and dermoscopic characteristics of genital melanocytic nevi in children, 2 more cases of Spitz nevi on the labia majora have been reported [6]. In adult patients spitzoid lesions may pose diagnostic difficulties as melanoma may mimic Spitz nevi from a morphological point of view. Melanoma is the second most common malignancy of the vulva after squamous cell carcinoma. It generally affects postmenopausal women, with a peak incidence in the sixth and seventh decades of life, but can also affect younger women [4]. Primary vulvar melanoma most frequently develops on the labia majora, followed by the labia minora and clitoral hood. Roughly half of vulvar melanomas arise on glabrous (mucosal) skin, 38% at the hairy-glabrous skin junction, and 13% on hairy skin of the external genitalia [6].

Conclusions

In presence of new onset pigmented papules or nodules in the genital area of women, melanoma should be included in the differential diagnosis and especially in those older than 50 years, histological examination should be performed to rule out melanoma. In this report, given the peculiar area, recent onset, rapid growth and dermoscopic features, surgical excision was warranted. Our case highlights the importance of assessing the genital region during routine skin cancer screening examination, with particular attention about any new or changing lesions.

References


Rhinofacial entomophthoromycosis or zygomycosis is a rare infection, caused by *Conidiobolus coronatus* involving the nasal cavity, paranasal sinuses, and soft tissues of the face. It initially starts as a painless swelling of the rhinofacial region which is locally invasive and can lead to facial disfigurement over time [1]. The disease tends to involve immunocompetent males, usually involved in agriculture between the age of 20-50 years. The diagnosis is established through histopathological and mycological examination. Special stains like periodic acid schiff and silver methanamine can help in the visualization of fungal hyphae and confirmation of diagnosis. Herein, we present a case of rhinofacial entomophthoromycosis and describe the dermoscopic findings seen in the patient.

**Case Presentation**

A 19-year-old male, a farmer by occupation from the Himalayan region of north India, presented with diffuse facial swelling which initially started as nasal mass, gradually progressing to involve the upper half of the face including nose, cheeks, and forehead with significant facial disfigurement for 8 months. There were no other symptoms associated with the swelling. The patient had taken multiple short courses of antibiotics and antifungals without improvement. General physical and systemic examination of the patient was normal. Upon mucocutaneous examination, diffuse skin-colored to erythematous, slight scaly, woody hard, lobulated subcutaneous swelling was present over the nose extending to involve the center of forehead, upper part of both the cheeks, inner canthus of the eye, and infraorbital area restricting the patient’s vision (Figure 1A). Laboratory examination including blood count and blood chemistry were within normal limits. ELISA assays for detection of Human immunodeficiency virus and hepatitis B surface antigen were negative. Computed tomography scan revealed heterogeneously enhancing soft tissue mass in the left nasal cavity arising from inferior turbinate extending into the soft tissue of nasal septum. Dermoscopic examination (x10, polarized non-contact mode) was done which revealed focal yellowish-orange structureless area, dotted and linear vessels over a background of diffuse erythema.
Histopathological examination was done from the skin and underlying nasal mass. Skin biopsy revealed epidermal acanthosis, follicular plugs, and multiple epithelioid granulomas in the dermis with eosinophilic infiltrate (Figure 2, A and B). The nasal biopsy displayed amorphous eosinophilic material around fungal hyphae along with acute inflammatory infiltrate (Figure 2C). Gomori methanamine silver stain performed on the nasal biopsy sample demonstrated broad, aseptate fungal hyphae, a few branching at the right angle (Figure 2, D and E). No organism could be grown on tissue culture. A final diagnosis of rhinofacial entomophthoromycosis was made. The patient was started on itraconazole 200 mg twice a day and potassium iodide five drops 3 times a day.

**Discussion**

The clinical appearance of rhinofacial entomophthoromycosis can mimic neoplasms like subcutaneous malignant, lymphatic oedema, tuberculosis. Dermoscopy-based differential diagnosis of the present case include cutaneous tuberculosis, other deep mycosis like cutaneous sporotrichosis, though clinical appearance can help distinguish rhinofacial entomophthoromycosis from the latter. Timely diagnosis of this rare disorder is important to initiate early intervention and thus reduce patient morbidity. Application of dermoscopy has lately expanded to the diagnosis of deep fungal infections, though available literature is still limited [2]. To the best of our knowledge, dermoscopy of rhinofacial entomophthoromycosis has not been previously described. Generalized erythema, yellowish structureless area, presence of vessels, and white scar-like areas have been seen to be common dermoscopic features of deep mycosis [2]. The yellow follicular plugs appreciated in the dermoscopy of the present case are akin to yellow tears described in cutaneous leishmaniasis and cutaneous sporotrichosis. The presence of yellowish-orange areas on dermoscopy reflect the underlying granulomas, yellow dots correspond to dilated infundibulum present on histopathology, whereas white areas represent dermal fibrosis, with generalized erythema and vessels secondary to the dermal inflammation and neoangiogenesis.
Conclusions

Dermoscopic findings of rhinofacial entomophthoromycosis include yellowish-orange structureless areas, erythematous background, white areas, follicular plus, scaling, linear and dotted vessels. Dermoscopy can act as a useful tool in the diagnosis of this rare disfiguring deep mycosis and further work is needed in this field to corroborate findings seen in the present case.

References

Dermoscopic Findings of Recurrent Herpetic Whitlow in a Child

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Key words: Dermoscopy, Herpetic whitlow, Viral infection, HSV, Vesicular lesion.

Introduction

HSV-1 and 2 infections in children commonly present with fever and gingivostomatitis [1]. Infection of the fingers and toes, due to autoinoculation from asymptomatic salivary carriers, is known as Herpetic whitlow. Classically, it presents as deep seated, tender, non-purulent, swollen, vesico-ulcerative lesions on the finger, usually preceded by a prorome of numbness, tingling or itching of the affected site [1]. However, atypical presentations may be often misdiagnosed. Timely diagnosis of the condition helps prevent secondary bacterial infection. We report this case to emphasize the dermoscopic features of herpetic whitlow which has never been previously reported.

Learning Points

1. Herpetic whitlow can have ambiguous presentation and is commonly misdiagnosed.
2. Dermoscopic description of herpetic whitlow is characteristic and may help to avoid biopsy or serological test in children.
3. Specific diagnosis is made by PCR, can be aided by cytology.

Case Presentation

A 10-year-old girl presented with a 4 day history of redness, swelling and blistering of 2 fingers of the left hand. Patient gave a history of similar episode 2 years back over the same location. There was no history of fever, trauma, new medication, friction over the fingertips or any contact with other infectious lesions. On examination there were tense, clear, fluid-filled vesicles arranged linearly over the palmar side of the left thumb and index finger (Figure 1). Draining lymph nodes were not palpable. There were no coexisting mucocutaneous vesiculation. A clinical diagnosis of herpetic whitlow was made.

On dermoscopic evaluation, the lesions were longitudinally oriented and the primary lesions rested on a pale base with surrounding bright erythema. The primary lesions appeared as relatively pale rings circumscribed by a rim of red dots. The pale lobulated appearance is explained by the formation of intraepidermal bullae due to pathogenic ballooning degeneration of keratinocytes and acantholysis. The pallor is also partly due to the presence of vesicular fluid. The red dots
Differential diagnosis of herpetic whitlow includes bacterial infective whitlow, friction blister, suction blister, bullous impetigo, erythema multiformae, coxsackie virus infection [1]. Herpetic whitlow is a self-limiting infection and incision and drainage are not indicated, as they are done in bacterial paronychia, due to the risk of viremia and secondary bacterial infection. Treatment with antiviral decreases the duration of symptoms of viral shedding.

Conclusions
Diagnosis of herpetic infection is often made clinically. However, it resembles many other infectious and non-infectious dermatoses [1]. Our report documents the dermoscopic features of herpetic whitlow, which has never been previously reported and can aid in early diagnosis.

Consent: A written consent was taken from the guardian for using the image and other clinical information to be reported in the journal. The patient understand that their name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

References

Figure 1. Clear, fluid-filled vesicles over an erythematous base arranged in a linear fashion over the thumb and index finger.

Tzanck smear of blister fluid showed multinucleated giant cells. Gram stain did not reveal any bacterial colonies. PCR assay was positive for HSV-1 virus, confirming the diagnosis. The patient was started on oral acyclovir 200 mg 5 times a day and patient completed a course of 5 days of therapy with complete resolution of skin lesions.

Differential diagnosis of herpetic whitlow includes bacterial infective whitlow, friction blister, suction blister, bullous impetigo, erythema multiformae, coxsackie virus infection [1]. Herpetic whitlow is a self-limiting infection and incision and drainage are not indicated, as they are done in bacterial paronychia, due to the risk of viremia and secondary bacterial infection. Treatment with antiviral decreases the duration of symptoms of viral shedding.

Conclusions
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References

Figure 2. (A,B) Primary lesion over a pale base and surrounding erythema. Pale rings circumscribed by rim of red dots and a central red hue, with no loss of dermatoglyphics.

Figure 1. Clear, fluid-filled vesicles over an erythematous base arranged in a linear fashion over the thumb and index finger.

Tzanck smear of blister fluid showed multinucleated giant cells. Gram stain did not reveal any bacterial colonies. PCR assay was positive for HSV-1 virus, confirming the diagnosis. The patient was started on oral acyclovir 200 mg 5 times a day and patient completed a course of 5 days of therapy with complete resolution of skin lesions.
Reactive Pigmentation of Skin Graft Mimicking a Lentigo Maligna Recurrence: a Case Report

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Key words: dermoscopy, neoplasm recurrence, skin pigmentation, scar


Accepted: August 30, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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Introduction

There is limited information on dermoscopy of recurrent hyperpigmentation in skin grafts following lentigo maligna (LM) excision, especially in facial locations. We present a case with highly suspicious dermoscopic features of local recurrence of LM within the skin graft.

Case Presentation

A 49-year-old woman consulted with a 3-year history of hyperpigmented lesion on the left cheek, with gradual growth and darkening in the last 11 months. Physical examination revealed phototype IV and an 15-mm diameter brown macule. Dermoscopic evaluation (3Gen – DermLite DL4®) showed a pseudo-network with asymmetric pigmented follicular openings (Figure 1, A and B). Incisional biopsy was performed and confirmed the diagnosis of LM. Wide local excision with 5-mm margin was performed, followed by immediate reconstruction with a retro-auricular split-thickness skin graft. Histopathologic examination confirmed the diagnosis of LM, without ulceration, mitosis, nor lympho-vascular invasion, and with clear surgical margins. At a 3-month follow-up, the patient reported recurrent pigmentation within the scar. Physical examination revealed an erythematous scar with a brown pigmented border, 13 x 10 mm in diameter (Figure 1C). Dermoscopic evaluation showed brown pigmented areas extending slightly beyond the edge of the graft, with a pseudo-network pattern, asymmetric pigmented follicular openings and circles within circles, predominantly in the upper lateral area (Figure 1D). Recurrent LM versus reactive graft pigmentation were the proposed diagnosis. A new biopsy was performed, with complete excision of the scar, and histopathologic study ruled out malignant melanocytic neoplasia, with findings of dermal scarring, foreign body-type granulomas and dermal melanosis. SOX-10 staining showed normotypic melanocytes, adequate in number and size (Figure 2, A–C). Patient remains without signs of recurrence or pigmentation at the 6-months follow-up.
Conclusions

The most frequently described dermoscopic features of reactive pigmentations includes: a homogeneous radial band-like and continuous brownish lines that extends perpendicularly to the scar [1]. This case report describes unusual dermoscopic characteristics of reactive pigmentation within a skin graft, resembling a recurrence of LM. Circle within circle sign is associated with LM with an odds ratio of 6.32 [2]. In addition, hyperpigmentation exceeding the edge of the scar is considered one of the most important criteria to suspect recurrent melanoma.

In our case, the pattern of double circles associated with hyperpigmentation that exceeds the edge of the graft scar was observed, leading to suspect a recurrence of LM, which was histologically ruled out. We suggest that in grafts of the facial area in patients with darker skin phototypes, the underlying inflammation related to scarring would lead to reactive melanosis with a double circle pattern on dermoscopy as seen in LM recurrence in a scar. As reported by Navarrete-Dechent et al. in patients with scar tissue from previous treatment of LM, dermoscopy of melanoma-specific features has limitations [3], therefore, histopathological confirmation is essential for the differential diagnosis.

Figure 1. (A) Clinical appearance pretreatment. Hyperpigmented macula, 15 x 11 mm in diameter, on the left cheek. (B) Dermoscopy pretreatment. Brown macula, with pseudo-network structure. Loss of follicular openings is observed isolated in the periphery (arrows). Arboriform telangiectasias at the bottom of the lesion. (C) Clinical appearance after surgery. Erythematous plaque with a scar-like aspect and a brown pigmented border measuring 13 x 10 mm in diameter, on the left cheek. (D) Dermoscopy after surgery. In the center of the lesion: follicular openings can be seen forming whitish circles. In the periphery: brown pigmentation which exceed the edge of the scar with the appearance of a pseudo-network. In superior lateral region: structures in a double concentric circle (arrow).


References


Figure 2. (A) Histopathology examination (H&E, 4x) shows a slightly atrophic epidermis with basal hypermelanosis. Proliferation of fibroblasts in the dermis associated with a perivascular lymphohistiocytic inflammatory infiltrate and the formation of granulomas with multinucleated giant cells. (B) Higher magnification (H&E, 20x) shows basal hypermelanosis without proliferation of melanocytes. (C) SOX-10 staining shows melanocytes of adequate number and size, equidistant and normotypic.
Introduction

Differentiating human papillomavirus (HPV) folliculitis from molluscum contagiosum (MC) folliculitis over the beard area can be clinically challenging. Both can present as asymptomatic follicle-based papules, and the verrucous morphology of HPV infection and punctum of MC may not be appreciable in all cases.

Case presentation

The first case is a 26-year-old male who presented with a history of multiple asymptomatic lesions on the beard for 4 months. Cutaneous examination showed multiple follicle-based skin-colored to pearly-white papules (Figure 1A). Dermoscopic examination under nonpolarized mode showed perifollicular pearly white clods (Figure 1B). Histology of a papule showed lobular epidermal acanthosis with prominent intracytoplasmic Henderson-Patterson bodies, consistent with a diagnosis of MC folliculitis (Figure 1C).

The second case is a 33-year-old male who had multiple asymptomatic skin lesions over the beard for the last 6 months. He denied any history of recent cosmetic procedures. Cutaneous examination revealed multiple follicle-based skin-colored flat-topped (2 mm X 3 mm) papules (Figure 2A). Dermoscopy showed a perifollicular mosaic pattern comprising a variable-shaped white knob-like area with or without central dotted and hairpin vessels (Figure 2B). Histology of a papule showed basket weave hyperkeratosis, hypergranulosis, moderate acanthosis, and koilocytes in upper stratum spinosum and granulosum, consistent with the diagnosis of verruca plana/HPV folliculitis (Figure 2C).

In both the patients, all the investigations, including HIV 1 and 2 serology, to rule out immunosuppression were negative.
Conclusions

MC folliculitis is rare and usually occurs in patients with either acquired or iatrogenic immunosuppression. The presence of flesh-colored to erythematous papules with or without central umbilication is the common presentation. HPV can spread from infected materials during cosmetic procedures, resulting in cosmetic warts. It can also spread along the line of the trauma due to pseudo-Koebnerization of preexisting warts [2]. The case in the discussion was unique. Each of the flat-topped papules over the beard area was follicle-based compared to the clustered or linear arrangement described for cosmetic warts or pseudo-Koebnerization, respectively.

Under dermoscope, MC characteristically demonstrates a variable-shaped white clod and crown vessels with or without a central punctum. Other features described are rosette, dotted and radial vessels [1,2]. Verruca vulgaris demonstrates grouped papillae with dotted and hairpin vessels surrounded by a whitish halo. In contrast, the verruca plana can have dotted vessels on a yellowish background [1]. We observed a mosaic pattern comprising a white knob-like area with or without a central hairpin or dotted vessel in the HPV folliculitis.

The dermoscopic features described for other infectious folliculitis are the following: dotted vessels in Malassezia folliculitis; broken hairs, corkscrew hairs, black dots, zigzag hairs, and morse code hairs in dermatophytic folliculitis; central round pustule with peripheral sparse dotted vessels in staphylococcal folliculitis; and Demodex tails, and Demodex follicular openings in Demodex folliculitis. Another common mimicker, pseudo-olliculitis, demonstrates a U-shaped in-growing hair under a dermoscope [1,2].

In conclusion, we report dermoscopic features of 2 rare cases of viral folliculitis on the beard. The dermoscopic examination can help differentiate between MC folliculitis.

Figure 1. (A) Multiple follicle-based skin-colored to pearly-white (arrow) papules. (B) Dermoscopic examination (Heine Delta20®, 10X magnification) showing perifollicular pearly white clods. (C) Histology shows endophytic epithelial hyperplasia containing molluscum bodies (H & E, X50).

Figure 2. (A) Multiple follicle-based skin-colored verrucous flat-topped papules. (B) Dermoscopy (Heine Delta20®, 10X magnification) shows a perifollicular mosaic pattern comprising of a variable-shaped white knob-like area with or without central dotted and hairpin vessels. (C) Histology shows basket weave hyperkeratosis, hypergranulosis, moderate acanthosis, and koilocytes in upper stratum spinosum and granulosum (H & E, X50). Inset showing koilocytes (H & E, X400).
from HPV folliculitis, with the former characterized by white clot and the latter by a mosaic pattern.

References


Metastatic Crohn Disease with Groin Localization in an Adult Patient

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Key words: metastatic Crohn disease, groin, adult, genital ulcers, granuloma

Citation: Gulseren D, Ersoy-Evans S. Metastatic Crohn’s Disease with Groin Localization in an Adult Patient. Dermatol Pract Concept. 2022;12(2):e2022056. DOI: https://doi.org/10.5826/dpc.1202a56

Accepted: August 30, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: Both authors have contributed significantly to this publication.

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Introduction

Metastatic Crohn disease (MCD) is a rare skin manifestation of Crohn disease (CD). MCD can develop on any cutaneous surface, but has a predilection for the genital region, especially in children [1]. Herein, we present an adult case of MCD with groin localization, so as to highlight the fact that this localization can easily be overlooked if patients do not present with any gastrointestinal symptoms.

Case Presentation

A 58-year-old male presented with a painful ulcer that had appeared on his right groin 10 days earlier. He did not report having any systemic diseases or systemic symptoms involving the gastrointestinal system. Upon dermatological examination there was a linear, 1.3 cm × 5 cm tender ulcer on his right groin. The ulcer was rather deep and extended to the subcutaneous tissue, forming a fistulous tract. A swab culture of the discharge showed Enterococcus faecalis, Enterococcus faecium, Escherichia coli, and Klebsiella pneumoniae growth; therefore, parenteral sulbactam-ampicillin therapy was initiated. Despite the lack of high-risk sexual behavior, doxycycline was empirically added to the patient antibiotic regimen for lymphogranuloma venereum infection, but the ulcer did not improve. A skin punch biopsy sample was obtained from the edge of the ulcer and histopathological analysis showed suppurative granulomatous inflammation. Histological stains were negative for bacterial and fungal microorganisms. Following histopathological examination, cutaneous tuberculosis, deep fungal infection, tularemia, and syphilis, which can lead to granuloma formation, were ruled out via additional detailed tests, including skin culture, PCR, and serological tests.

To assess the connection of the ulcer, fistulography was performed, which showed distribution of the radiocontrast agent in several tracts between soft tissues. Abdominal computed tomography scan showed terminal ileitis and a fistula extending to the skin, although the patient did not report any gastrointestinal symptoms relating to the diagnosis of CD. Colonoscopy and colonoscopic biopsy were performed, and the findings were consistent with active colitis. Based on the clinical, radiological, colonoscopic, and histopathological findings, the patient was diagnosed with MCD. After
starting oral mesalazine, azathioprine, and prednisolone, the fistulous discharge decreased, but the ulcer did not heal completely (Figure 1); consequently, fistulectomy and right hemicolectomy were performed.

Discussion

MCD is the least common dermatologic manifestation of CD. In 70% of adult patients MCD lesions appear after the initial diagnosis of CD; therefore, its diagnosis can be challenging in adults without active gastrointestinal symptoms at presentation [2]. The presented patient did not have any gastrointestinal symptoms, which delayed the diagnosis of MCD. Another challenging aspect of diagnosis is ulcer localization. Although the most common presentation of MCD in children is the genital region, the most common presentation in adults is the extremities. Genital localization is of particular importance in sexually active adult patients, as it can mimic sexually transmitted diseases.

Conclusions

MCD is a rare cause of genital ulcers in adult patients and can present without gastrointestinal symptoms. Genital ulcers with granuloma formation in adults should suggest MCD, even in patients that do not report any gastrointestinal symptoms.

References

Recurrent Acute Generalized Exanthematous Pustulosis to Two Different Drugs: Oxacillin and Dextromethorphan Confirmed by Patch Test

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Key words: Acute generalized exanthematous pustulosis, oxacillin, dextromethorphan, recurrence, patch test

DOI: https://doi.org/10.5826/dpc.1202a58

Accepted: August 24, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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Introduction

Acute generalized exanthematous pustulosis (AGEP) is a potentially severe skin condition, mainly drug induced [1]. Recurrences are rare and generally induced by related drugs. Dextromethorphan is an antitussive agent which is unusually reported as culprit in AGEP. Herein we report a rare case of relapsing AGEP to dextromethorphan and oxacillin.

Case Presentation

A 32-year-old woman, with a history of a controlled generalized pustular psoriasis, presented to our department with a 4 day history of fever with predominately flexural eruption of non-follicular pustules on a erythematous background, which had started 2 days after the intake of oxacillin and tiaprofenic acid. Investigations found an elevated absolute neutrophil count and skin biopsy demonstrated histologic features consistent with AGEP. Skin lesions totally resolved within 10 days after oxacillin discontinuation. A patch test with oxacillin and tiaprofenic acid (the commercialized form used by the patient diluted to 30% pet.) was performed and showed a +++ skin reaction to oxacillin on day 4 but no reaction to tiaprofenic acid. All penicillins were prohibited.

Two years later the patient presented with a similar eruption and fever 4 days after taking 2 multi-compound medications named goldix day (dextromethorphan, doxylamine, paracetamol) and goldix night (dextromethorphan, paracetamol, phenylephrine) for a cold (Figure 1). She denied taking any other drug. Complete blood count showed
marked neutrophilia and skin biopsy was consistent with AGEP. Diagnosis was defined following EuroSCAR criteria. Patch testing with the component of the commercialized package of goldix day (30% pet.), goldix night (30% pet.) and paracetamol (50% pet.) was performed. The patch test preparations were applied in IQ Ultra (Chemotechnique Diagnostics). The patch tests were occluded for 48 hours, and readings were performed according to ICDRG/ESCD criteria on day 2 and day 4. Patch testing showed a ++ skin reaction to goldix day and goldix night, but was negative to paracetamol (Figure 2). The oral provocation test to paracetamol was also negative. The constituent dextromethorphan was not available for testing, but was suspected as the cause of the reaction as it was the only compound in common besides paracetamol. We performed a genetic analysis to determine whether there was mutation of the IL36RN gene, as it may be a predisposing factor, but we did not find such mutation in our patient.

Conclusions

Recurrences in AGEP are rare and often induced by related drugs, mainly B-lactams. Our case suggests that it may be induced by chemically different medications in potentially predisposed patients possibly having pattern of cytokine dysregulation. Indeed, it seems that psoriasis might be a risk factor of relapsing AGEP. We have also shown that IL36RN gene mutation does not fully explain the pathogenesis of pustular generalized eruptions. Moreover, our observation is notable for the implication of dextromethorphan, a widely used opioid antitussive agent, as a culprit drug. To the best of our knowledge, only 1 case of AGEP induced by dextromethorphan and confirmed by patch testing has been previously reported [2].

References

Sanitizing Hand Gels: a Potential Source of Burn in the Covid-era

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Key words: burn, hand sanitizing gel, SARS-CoV-2, skin allografts.

Introduction

The SARS-CoV-2 pandemic has brought new challenges to the world. To limit virus spread, effective hand hygiene is crucial. WHO’s recently recommended healthcare workers to perform hand hygiene at 5 crucial moments (before touching a patient, before aseptic procedures, after body fluid exposure, after touching a patient or surroundings), and generally before putting on/after removal of positive protective equipment, before food preparation and eating and after using the toilet.

Case Presentation

An otherwise healthy 43-year-old woman came to our dermatological emergency room with a burn injury in both hands, first treated with topical antibiotics dressing for 48 hours.

Clinical examination (Figure 1) revealed second and first degree burns involving both palms, volar surface of the wrists and the back of her right hand (ie 2% of TBSA). Clinically, the injury was mid-dermal in depth. The incident occurred when the patient lightened a cigarette just after having performed hand hygiene with a commercially available hand sanitizing gel. The patient noticed a blue flame over the site of gel application and was able to extinguish it by rapidly immersing both hands into cold water. The burn was managed orally with amoxicillin-clavulanate for 1 week and oral analgesics. Patches of cryopreserved skin allografts were applied on the thenar eminence grade 2 burned areas for 7 days, followed by hyaluronic acid gauzes for 7 days, and hyaluronic acid cream for further 7 days.

Complete healing with moderate post-inflammatory dyspigmentation was observed after 21 days (Figure 2). The sanitizing hand gel was composed of: denatured alcohol, triethanolamine, benzyl salicylate glycerin, carbomer, o-phenylphenol, parfum, aqua.

Discussion

Some concerns have been previously raised about the flammability characteristics of hand sanitizers gels [1]. Indeed, alcohol-based hand sanitizers should contain between 60% and 80% of alcohol (usually ethanol or methanol) to be
effective: these alcohols can easily ignite and tend to burn relatively coldly. Moreover, the vapor produced on the hands after gel application is flammable [2]. From March 2020, everyone has started using hand sanitizing gel in daily life, either for the recommendations and for their large availability at the entrances not only in hospitals, healthcare institutions and pharmacies, but also in every public shop and working place. This widespread use has caused an increase in irritant/allergic contact dermatitis cases, either relapsed or newly developed, and generally a worsening of atopic eczema and dryness.

Conclusions

In the Covid era, the danger related to the flammable nature of hand sanitizing gels has yet not been stressed, and the occurrence of burns after cigarette lightening following sanitizing gel application never reported. Nevertheless, healthcare workers, non-healthcare workers and the general public are usually not aware, or not used to wait until the product as completely dried on the skin surface in daily life. People should now be informed on the flammability danger and should be aware of the necessity to wait few minutes to respect adequate time before getting close to ignition sources (eg cooking) or touching metal surfaces.

References

Secret of The “White Belly Button” During Pregnancy Demystified

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Key words: hypopigmentation, pregnancy, depigmentation, belly


Accepted: September 2, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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Introduction

During pregnancy, several physiological, hormonal, immunological, metabolic and vascular changes occur [1]. The skin is one of the first organs that may be affected. We report a case of a sudden whitish macular eruption on the belly that occurred at 30 weeks of pregnancy.

Case Presentation

A 33-year-old female patient with no particular medical history at 36 weeks of pregnancy developed a white macule with irregular borders on the belly with a downward extension which has occurred 6 weeks before (Figure 1) (Figure 2). The patient didn’t complain about itch or pain, and no sclerosis or scales were present on physical examination.

Conclusions

Pregnancy dermatoses are classified into: structural skin changes, specific dermatoses of pregnancy and preexisting...
dermatosis of pregnancy [2]. A rare condition characterized by the presence of a whitish macular eruption of the belly is often a cause of concern in pregnant women. The “white belly button” is a benign physiological phenomenon; it appears as a sudden demarcation of “white areas” or a “skin pallor” that affects the skin due to a vascular abnormality resulting from an excessive stretching of the skin. The abrupt onset of this macule has never been described or reported in any scientific journal and the physio-pathological mechanism remains unknown but can be explained by the presence of a tissue hypoxia as a result of vasoconstriction of small dermal vessels.

It is therefore important to differentiate this physiological pigmentation from other skin conditions such as post inflammatory hypopigmentation, vitiligo, nevus depigmentosus pityriasis versicolor and white spot disease to avoid unnecessary treatment and to reassure pregnant women about the benignity of this condition.

References

Dermoscopic Keys in Extragential Bullous Hemorrhagic Lichen Sclerosus

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Key words: lichen sclerosus, hemorrhagic, dermoscopy, follicular plugs

Citation: Mani S, Oberoi B. Dermoscopic keys in extragenital bullous hemorrhagic lichen sclerosus. Dermatol Pract Concept. 2022;12(2):e2022063. DOI: https://doi.org/10.5826/dpc.1202a63

Accepted: September 22, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: Both authors have contributed significantly to this publication

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Introduction

Lichen sclerosus (LS) is a chronic inflammatory dermatosis characterized by leukoderma and scarring, predominantly affecting the genital skin. It may sometimes involve extragenital areas. The suffix atrophicans is no longer used as a few cases are associated with hypertrophy rather than atrophy. Few atypical variants include bullous, hemorrhagic, pigmented, verrucous, and keratotic forms. Herein, we report a case of extragenital bullous hemorrhagic lichen sclerosus with its dermoscopic features.

Case Presentation

A 40-year-old male presented with a nine-month history of a slow-growing asymptomatic raised lesion on his back associated with occasional bleeding episodes after casual trauma. There was no history of similar lesions in the past or elsewhere on the body. Physical examination revealed a solitary, well-defined, 2.5 cm × 2.0 cm, non-tender, hemorrhagic bulla with crusting in the center and atrophy in the surrounding area (Figure 1A). Dermoscopy revealed superficial yellowish white and hemorrhagic crusts, follicular plugs, and multicolored diffuse hemorrhagic area with varying shades ranging from black to red, with black color representing old hemorrhage and red color representing recent hemorrhage (Figure 1B). Surrounding skin revealed atrophy with follicular plugs (Figure 1C). Based on the clinical and dermoscopic examination, we considered hemorrhagic lichen sclerosus, irritated seborrheic keratosis, Bowen disease, and discoid lupus erythematosus as our differential diagnoses. Histopathology revealed follicular plugs, epidermal atrophy, subepidermal blister, and hyalinized compact collagen, which confirmed the case to be LS (Figure 1D).

Discussion

The extragenital form of LS is less common, and the bullous hemorrhagic form is very rare, with only a handful of cases in the literature. This form is generally associated with less pruritus and the absence of any malignancy, as seen in our patient as well. In our case, the lesion was present on the back, a site that has not been reported for this particular variant. The formation of bullous lesions has been described...
in LS. A possible explanation for the formation of bulla and hemorrhage could be the pronounced edema within the skin that disrupts the capillaries collagen support, predisposing them to rupture with minimal trauma or damage [1].

Conclusions
Dermoscopy of extragenital LS has been described as white structureless areas, follicular plugs, white chrysalis-like structures, and variable vascular patterns being the essential components [2]. Our case had superficial yellowish white and hemorrhagic crusts, a multicolored (black to red) hemorrhagic area, and a peripheral atrophic area with follicular plugs. There was no vascular pattern which commensurates with the chronicity of the lesion. The patient was managed with topical corticosteroids with a good response. This case report helps establish the fact that follicular plugs which have been reported in LS are seen in this rare variant also. In addition, the dermoscopic features of the hemorrhagic area of LS, which have not been previously described, have been
brought out. This report will enhance the existing repertoire of knowledge of dermoscopic features of LS which may aid diagnosis in future and avoid invasive procedures.

References


Cutaneous Involvement of Mantle Cell Lymphoma: Report of Two Cases with Dermatoscopic Features

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Key words: mantle cell lymphoma, dermatoscopy, dermoscopy, prognosis, serpentine vessels

Citation: Akay BN, Farabi B, Atak MF, Kuzu I, Heper AO. Cutaneous Involvement of Mantle Cell Lymphoma: Report of Two Cases with Dermatoscopic Features. Dermatol Pract Concept. 2022;12(2):e2022064. DOI: https://doi.org/10.5826/dpc.1202a64

Accepted: September 6, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Mantle cell lymphoma (MCL) is a rare aggressive B-cell lymphoma and represents 6% of all non-Hodgkin lymphomas. Cutaneous involvement (CI) of systemic MCL is rarely reported and is related to poor prognosis. Skin involvement in systemic lymphomas (SLs) can be challenging. Dermatoscopy may serve as a useful tool to diagnose and ameliorate the prognosis by leading early diagnosis. In this context, we present two cases of MCL with secondary CI, who presented with widespread plaques and nodules and describe their dermatoscopic features.

Case Presentations

The first patient was a 73-year-old male diagnosed with MCL in 2014. He referred to dermatology department for asymptomatic pink-red colored generalized skin lesions in August 2018 (Figure 1A). Dermatoscopic examination showed pink white structureless lesions with unfocused thick serpentine vessels (Figure 1B). Second patient was a 66-year-old female diagnosed with MCL in 2017, admitted for multiple nodular lesions developed on the trunk and extremities in January 2019 (Figure 1C). Dermatoscopic examination showed thick serpentine-branched and reticular vessels on whitish-pink violaceous background (Figure 1D). Both lesions were biopsied and showed similar features including diffuse infiltration of the mid and deeper dermis with medium-sized lymphocytes with irregular nuclei. The tumor cells were positive for CD5, CD20, CD79a, cyclin D1, and negative for CD10 (Figure 2). Both patients were diagnosed with CI of MCL. They have been treated with combined chemotherapy regimens including rituximab, unfortunately both patients were deceased due to disease dissemination (14 months and 18 months after CI, respectively).
Discussion

MCL originates from primarily lymph nodes and extra-nodal organs (bone marrow, spleen, gastrointestinal tract). Skin involvement portends a poor prognosis and is seen in 2% of the cases. Previously, 24 cases of secondary CI of MCL have been reported.

The value of dermatoscopic examination in cutaneous lymphomas (CL) have been proposed in previously published studies. A recent systematic review regarding dermatoscopic findings in primary CLs showed that dermatoscopy assisted skin biopsies ensure early diagnosis based on the findings such as salmon-colored background, fine short/linear irregular serpentine vessels, scale, and white areas/circles [1]. Regarding the dermatoscopic features of secondary CI of SLs, only 1 case of MCL has been reported and showed multiple chaotically distributed short linear vessels with multiple red dots within hair follicles on a whitish background. As the lesion progressed, wider telangiectatic vessels on a reddish background were observed, and the lesions regressed under treatment [2]. We observed pink and white structureless lesions with unfocused thick short serpentine vessels in flat lesions, as lesions became nodular as in our second patient, the vessel calibers increased, branched and reticular vessels were observed on purple-pink, white background which is hypothetically due to increased tumor volume and expansion of the dermis by malignant infiltrate.

Conclusions

Skin involvement in MCL suggests poor prognosis. Though, dermatoscopic features are not specific to CI of SLs, they can raise suspicion to biopsy these lesions in earliest stages.


**Figure 2.** Histological and immunohistochemical findings of the papules from case 2. (A) Diffuse proliferation of small atypical lymphoid cells with fine chromatin (H&E x10). The subcutaneous atypical lymphoid cells were expressing strong CD20 (b) and CD5 (c), pale IgD(d). (E,F) The cells were specifically negative for CD3 (e) and positive for cyclin D (f).
Rosette or Four Dot Signs in Dermoscopy: a Non-specific Observation
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Key words: dermoscopy, four dot, actinic keratosis, lichen planus, perniosis, lichen sclerosus et atrophicus

Citation: Jindal R, Chauhan P, Shirazi N. Rosette/ four dot sign in dermoscopy: A non-specific observation. Dermatol Pract Concept. 2022;12(2):e2022069. DOI: https://doi.org/10.5826/dpc.1202a69

Accepted: October 6, 2021; Published: April 2022

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Funding: None.
Competing interests: None.
Authorship: All authors have contributed significantly to this publication.
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Introduction
Rosettes or four dot signs in dermoscopy are described as 4 bright white dots or globules grouped like a four-leaf clover. They vary in size from 0.2 mm to 0.5 mm and can be oriented in the same angulation or different angulation. These have been characteristically described in squamous cell carcinoma and actinic keratosis [1]. However, there have been anecdotal reports of their presence in melanoma, basal cell carcinoma, dermatofibroma, molluscum contagiosum, lichen planus like keratosis, discoid lupus erythematosus, and pigmented purpuric dermatoses [2]. Their definite histopathological correlate has not been elucidated. The explanation accepted by most clinicians is that they represent the optical effect between polarized light and follicular structures. Polarizing horny material at the infundibular level in adnexal openings and peri-follicular fibrosis results in smaller and larger rosettes, respectively.

Case Presentation
The present case series describes 5 diseases (in 5 patients) where rosettes were seen, suggesting that they would be non-specific. These were lichen sclerosus, lichen planus, perniosis, apocrine hidrocystoma, and photo contact dermatitis (Figures 1-5). Diagnoses were confirmed histopathologically, and a possible dermoscopy correlation with observed histopathology was established (Table 1).

Conclusions
Rosette sign in dermoscopy is not disease-specific as was once presumed. Although it is observed in high frequency in actinic tumors like actinic keratosis and squamous cell carcinoma, several unrelated inflammatory and papulosquamous diseases also exhibit it. Its most likely explanation is the interaction of keratin filled adnexal openings with the polarized light.
Figure 1. (A) Multiple white rosettes (blue circle, Dermlite DL200 hybrid, 10x magnification [3Gen]. (B) Multiple white atrophic plaques over leg. (C) Hyperkeratosis, epidermal atrophy with basal vacuolar degeneration, papillary dermal edema and underlying lymphocytic infiltrate (H&E, ×10).

Figure 2. (A) Multiple white rosettes (blue circle). (B) Erythematous to violaceous plaques over trunk and extremities. (C) Hyperkeratosis with keratin filled craters, basal vacuolar degeneration and dense band like lymphocytic infiltrate at dermo-epidermal junction (H&E, ×10).

Figure 3. (A) White rosettes (blue circle). (B) Erythema and edema over toes. (C) Hyperkeratosis, follicular plugging, dermal edema and perivascular as well as peri-eccrine lymphocytic infiltrate (H&E, ×10).
Table 1. Demographic profile, clinical features, and dermoscopy-histopathology correlation in 5 cases with rosette sign.

<table>
<thead>
<tr>
<th>Figure (Case) #</th>
<th>Age (years)/ Gender</th>
<th>Clinical presentation</th>
<th>Duration</th>
<th>Histopathological diagnosis</th>
<th>Dermoscopy correlation with histopathology for rosettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>18/male</td>
<td>Multiple white atrophic plaques over left leg</td>
<td>2 years</td>
<td>Lichen sclerosus et atrophicus</td>
<td>Follicular plugging</td>
</tr>
<tr>
<td>#2</td>
<td>22/ female</td>
<td>Multiple, itchy erythematous to violaceous plaques over trunk and extremities</td>
<td>2 months</td>
<td>Lichen planus</td>
<td>Hyperkeratosis with sharp depressions giving the appearance of keratin filled craters</td>
</tr>
<tr>
<td>#3</td>
<td>20/ female</td>
<td>Erythema and edema over toes</td>
<td>4 days</td>
<td>Perniosis</td>
<td>Hyperkeratosis with wavy margin and peri-eccrine inflammation</td>
</tr>
<tr>
<td>#4</td>
<td>30/ male</td>
<td>Skin-colored to bluish nodules coalescing to form a plaque over the neck</td>
<td>10 years</td>
<td>Apocrine hidrocystoma</td>
<td>Hyperkeratosis with follicular plugging and peri-follicular fibrosis</td>
</tr>
<tr>
<td>#5</td>
<td>60/ male</td>
<td>Bright red plaques over dorsae of hands</td>
<td>7 days</td>
<td>Photo-contact dermatitis</td>
<td>Parakeratosis scale filling the sweat duct openings.</td>
</tr>
</tbody>
</table>

Figure 4. (A) Multiple white rosettes (blue circle). (B) Skin colored to bluish nodules coalescing to form a plaque over the neck. (C) Hyperkeratosis, follicular plugging with peri-follicular fibrosis, multiple dermal cystic spaces lined by a bilaminar epithelium with apocrine snouts at places (H&E, ×10).

Figure 5. (A) White rosettes (blue circle). (B) Bright red plaques over dorsae of hands. (C) Parakeratosis with follicular plugging, spongiosis, dermal edema and peri-vascular lymphocytic infiltrate (H&E, ×10).
References


Birth of a Melanoma

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Key words: dermoscopy, melanoma, total body photography, dermatopathology

Introduction

Early melanoma diagnosis is a major prognostic factor for improved patient survival. Since its introduction in the dermatological practice, total body photography has proven to be a powerful tool for uncovering new or changing pigmented lesions that are either too small or unremarkable during a routine clinical skin exam in high-risk individuals [1]. Thanks to this technique, the number of reported melanomas measuring less than 2 mm in diameter, defined as micro-melanomas, is increasing. Consequently, the relevance of the 6 mm size criterion of the classic ABCDE rule is currently under question [2].

Case presentation

A 29-year-old man with a personal history of melanoma consulted our clinic for his annual skin exam and total-body-photography. The comparative photography revealed a new, tiny, pigmented lesion on his right lateral trunk, measuring 1.0 mm x 1.5 mm, and appearing darker than the rest of his naevi (Figure 1, A and B). The digital dermoscopy exam revealed an atypical melanocytic lesion, characterized by asymmetry, and irregular network composed of non-uniform streaks of uneven width and borders. There was expansion in an asymmetrical starburst pattern with melanocytic projections of variable sizes and bulging ends with no connection to the lesion, predominating in one extremity of the lesion, and corresponding to pseudopods (Figure 1C). The lesion was excised and the histopathological analysis revealed an asymmetrical junctional melanocytic proliferation with nests of various sizes composed of large epithelioid melanocytes with cytologic atypia; pleomorphic nuclei, dusky and heavily pigmented cytoplasm, and mitotic figures. There was focal lentiginous proliferation in connection with a peripheral nest, compatible with the horizontal expansion seen in the dermoscopic image of irregular streaks, as well as isolated melanocytes in a pagetoid scatter (Figure 2). Two dermatopathologists reviewed the specimen. Given the lentiginous spread extending over 3 papilla in the periphery of the lesion, and the pagetoid ascension, which was limited over the nests in the center of the lesion, the diagnosis of melanoma in situ, acral lentiginous subtype, was retained. A re-excision of the scar with 5 mm lateral margins and up to the muscle fascia was performed. We are currently following the patient alternating clinical exam and total body photography every 6 months according to the Swiss Melanoma guidelines.
Figure 1. Total Body Photography exam: a new lesion is identified during time-lapse comparison of photos. (A) Total-body-photography at visit 1. (B) Total-body-photography at visit 2, one year later revealing the presence of a new melanocytic lesion. Inset: high power of the new lesion showing a darker pigmentation than the rest of the nevi. (C) Digital dermoscopy of the new lesion showing an atypical melanocytic network with irregular streaks and pseudopods in an asymmetrical starburst pattern dominating one extremity of the lesion.

Figure 2. Histopathology correlate revealing features of melanoma in situ. (A-D) 10x magnification sections in different levels of the lesion depicting the asymmetrical melanocytic growth with junctional nests of various sizes, distributed unevenly. (E) 40x magnification of the B section showing the lentiginous spread in contact with a peripheral nest, corresponding to the pseudopods seen in dermoscopy. The melanocytes exhibit large nuclei compared to the neighboring keratinocytes with abundant cytoplasm, and heavy pigmentation in some of the cells. No pagetoid scatter was observed in the periphery of the lesion, compatible with an acral lentiginous subtype melanoma. (F) 40x magnification of a central nest with a mitotic figure (red asterisk). (G) 40x magnification of the D section showing interconnected nests in the center of the lesion with scattered melanocytes in the suprabasal layers of the epidermis (green asterisks), compatible with pagetoid ascension.

Conclusions

Although rare, acral lentiginous melanomas have been reported in non-acral sites and their dermoscopic features are similar to the ones observed in our patient. This case illustrates the success of time-lapse total body photography in the identification of melanomas, akin to witnessing the birth of a star, but also the fine correlation of dermoscopy and pathology. Furthermore, the systematic documentation of micro-melanomas with digital dermoscopy combined with digital pathology and the molecular and genetic profiling of the excised lesions constitute a great opportunity to study these very early events of malignant melanocytic expansion.

References


Introduction

Grafts-versus-host disease (GvHD) is a severe systemic complication most commonly occurring after allogeneic hematopoietic stem cell transplantation (HSCT). We would like to share our clinical experience with a patient who developed a grade 4 hyperacute GvHD after haploidentical HSCT for acute myelogeneous leukemia (AML).

Case Presentation

A 18 year-old woman with a history of haploidentical HSCT was consulted for palmoplantar erythematous rash and severe mucositis. Twelve days prior to the consultation, she had allogeneic haploidentical HSCT from her younger sister for AML. Three days after HSCT, the patient developed neutropenic fever and intractable diarrhea; intravenous (IV) meropenem, teicoplanin and metronidazole were initiated. There was no bacterial growth in blood and urine cultures. However, abdominal computed tomography revealed findings compatible with typhlitis. Twelve days after HSCT, she was referred to our clinic due to severe mucocutaneous eruption. Dermatological examination showed diffuse hemorrhagic-crusted plaques on her lips and neck and dusky-edematous plaques involving volar areas (Figure 1). Our initial diagnoses were Stevens Johnson syndrome (SJS), hyperacute grade 4 GvHD and paraneoplastic pemphigus. A skin biopsy was taken from the neck which showed mild lymphocytic
inflammation and vacuolar change at the epidermal-dermal junction, dyskeratosis in basal layer keratinocytes (Figure 2). Direct immunofluorescence assay was negative. She continued to have intractable diarrhea and gradually increasing levels of acute phase reactants, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and of total/direct bilirubin levels. Anti-skin specific antibodies were negative. With clinical, laboratory and histopathological findings, as the diagnosis was hyperacute grade 4 GvHD (the beginning of the rash was within the first week of HSCT) according to consensus grading of hyperacute/acute GVHD [1]. IV methylprednisolone was started as maintenance treatment. Cyclosporine and mycophenolate mofetil were switched to tacrolimus. Since SJS was could not be excluded on clinical grounds, recently administered antibiotic drugs teicoplanin and meropenem were changed to cefepime. However, she succumbed to death 5 weeks after HSCT.

**Discussion**

GvHD is a severe systemic complication most commonly occurring after allogeneic HSCT even though GvHD cases have also been reported in association with solid organ transplantation and non-irradiated blood product transfusion. Dermatological presentation may range from maculopapular eruption to generalized erythroderma and epidermal sloughing mimicking toxic epidermal necrolysis [1]. This severe dermatological presentation is accepted as stage 4 and grade 4
GvHD [1]. Schultz et al reported a case of grade 4 GvHD who developed extensive macular rash along with mucosal ulceration within weeks of liver transplantation [1]. Similar to the letter by Klein et al, our patient developed severe mucocutaneous eruption with epidermal sloughing within the second week of HSCT [2]. Distinctively, she had diarrhea and progressive elevation in bilirubin, ALP and GGT levels favoring the gastrointestinal involvement of acute GvHD.

**Conclusions**

In all patients with a prior history of allogeneic HSCT, hyperacute/acute GvHD should be considered in the differential diagnosis when severe mucositis, palmoplantar involvement, and epidermal detachment similar to SJS are observed.

**References**


Follicular Becker Nevus: an Unusual Clinical and Dermoscopic Manifestation

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Key words: Becker nevus, follicular, dermoscopy, papule

Citation: Zhang L, Shen X, Xu L, Shi H, Chen T. Follicular Becker’s nevus: an unusual clinical and dermoscopic manifestation. Dermatol Pract Concept. 2022;12(2):e2022074. DOI: https://doi.org/10.5826/dpc.1202a74

Accepted: September 8, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Becker nevus (BN) is characterized by a unilateral, hairy, pigmented macule usually involving the chest or scapular region. We hereby reported a specific case of follicular BN presenting follicular macules and maculopapules, and described its dermoscopic manifestation.

Case Presentation

A 20-year-old female presented with a 12-year history of multiple clustered asymptomatic brown macules and maculopapules affecting the inside of the left upper arm (Figure 1A). The pigmented lesions gradually increased in the initial phase and then stabilized. No other accompanied systemic abnormality was found. Familiar and medical histories were unremarkable. The dermoscopy revealed multiple brown round perifollicular macules with thicker hairs in the follicles (Figure 1B). The histopathological examination showed hyperkeratosis, acanthosis, and darkly pigmented basal cell layer (Figure 1C). A diagnosis of follicular BN was made.

Discussion

BN, also called pigmented hairy epidermal nevus, is characterized by a unilateral, hairy, pigmented macule usually involving the upper chest or the scapular region, a few cases present multiple or bilateral. The pathogenesis is still unclear. The plausible explanations for BN include mosaicism and an androgen-dependent lesion [1]. BN has male predilection, with a 2:1 to 5:1 predominance of men over women [1]. BN commonly appears during adolescence and some cases are congenital. The lesions usually present as an asymptomatic well-demarcated, irregular, brown macule with a geographic or block-like configuration. However, Manchanda et al first reported an unusual clinical manifestation of BN in 2020, which presented follicular lesions [2]. They speculated that some BN might begin from perifollicular lesions and follicular epithelium might hold a significant role in the etiopathogenesis. The mechanism of follicular BN and the pathogenesis of BN remain to be further studied.

BN usually do not require treatment, and some potential therapeutic options were taken due to cosmetic requirement,
including electrolysis, waxing, makeup, laser treatment, and topical therapy. Currently, no consensus has yet been reached in the literature regarding which treatment is preferred and success with each treatment varies widely.

Conclusions

Follicular BN is an unusual clinical variant. The dermatologist should be aware of the unusual clinical manifestation of BN, which could permit to quickly solve the clinical doubts and reassure the patient.

References


Vesiculobullous Erythema Elevatum Diutinum: a Rare Variant With Epidermolysis Bullosa Acquisita-like Immunofluorescence Findings

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Key words: Direct immunofluorescence, Epidermolysis bullosa acquisita, Erythema elevatum diutinum, Salt-split skin test

Citation: Yalici-Armagan B, Ates-Ozdemir D, Yeter G, Atakan N. Vesiculobullous Erythema Elevatum Diutinum: A Rare Variant with Epidermolysis Bullosa Acquisita-like Immunofluorescence Findings. Dermatol Pract Concept. 2022;12(2):e2022077. DOI: https://doi.org/10.5826/dpc.1202a77

Accepted: October 4, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Erythema elevatum diutinum (EED) is a rare, chronic dermatosis characterized by red-violet to red-brown papules, plaques, and nodules that favor extensor surfaces. Vesiculobullous variant is a rare form of EED [1]. Herein, we present a case of vesiculobullous EED with epidermolysis bullosa acquisita (EBA)-like with direct immunofluorescence (DIF) findings.

Case Presentation

A 65-year-old man presented with progressively increasing nodules on feet for 5 years, pruritic papules on knees and elbows for 1 year (Figure 1, A–E) and blisters on hands for 1 month. Dermatological examination revealed violaceous nodules on feet, erythematous flat-topped papules on elbows and knees with multiple tense blisters on palmar and dorsal region of hands. Hematoxylin and eosin staining from 2 punch biopsies of the foot and knee showed nodular and diffuse inflammation rich in neutrophils under uninvolved epidermis (Figure 2A). Small vessels are damaged by neutrophil-rich inflammation and leukocytoclastic debris, resulting in leukocytoclastic vasculitis (LCV) (Figure 2B) and storiform fibrosis at the dermis are consistent with EED. The biopsy of the hand dorsum demonstrated subepidermal separation with perivascular and interstitial inflammation rich in eosinophils with fibrin accumulation in the dermis (Figure 2, C and D). DIF from perilesional skin of the hand revealed linear deposition of immunoglobulins (IgG, IgA, IgM) and complement (C3) along the basal membrane zone (BMZ). Location of deposits were on the floor of the blister in salt-split skin test with IgG (Figure 2E). Full blood count showed iron deficiency anemia. Serology tests for HIV and hepatitis-B and C were negative. Dapsone was initiated 50 mg twice daily. At 5 weeks follow-up, a significant improvement
Figure 1. (A-E) Multiple tense blisters on palmar and dorsal region of hands (A,B); erythematous flat-topped papules on elbows and knees (C,D) and violaceous nodules on feet (E), improving of the vesiculobullous and papular lesions located on the hands (F,G) and knees (H).

Figure 2. (A-E) Diffuse dense inflammation composed of predominantly neutrophils and dermal fibrosis are observed under uninvolved epidermis. (A) Fibrin deposition is present around dermal vessels (H&E, 40x magnification). (B) Endothelial swelling, leukocytoclastic debris and fibrin deposition are visible in dermal vessels (H&E, 200x magnification). (C) Subepidermal separation is seen with fibrin deposition and mild to moderate perivascular and interstitial dermal inflammation (H&E, 40x magnification). (D) Subepidermal separation and mild to moderate inflammation are present with eosinophils (H&E, 200x magnification). (E) Linear IgG deposition is observed at the base of the split cavity (direct immunofluorescence with IgG in salt split skin, 200x magnification).
was observed in hands, knees and elbows (Figure 1, F-H), whereas there was a partial improvement in feet.

**Discussion**

EED is a rare skin disorder that is associated with a variety of systemic diseases. Histopathologically, it is characterized by early changes of LCV with an infiltrate of polymorphonuclear cells, occasionally eosinophils and deposition of fibrin which resolves with fibrosis. The association of EED and autoimmune bullous diseases, such as dermatitis herpetiformis (DH) has been described previously [2]. Recently, it is argued that these cases may be more compatible with vesiculobullous EED than with DH. Although, perivascular deposition of IgG, IgA, IgM, complement, and fibrin has been demonstrated in DIF examination of EED; granular IgA deposits with a pseudolinear pattern at BMZ was reported in a single case of vesiculobullous EED [1]. To our knowledge, this is the first case of vesiculobullous EED with linear IgA, IgG, IgM and C3 deposition in BMZ. The presence of the deposits in the base of the bulla in salt-split skin test was also a remarkable finding in the current case which could be a pitfall for EBA in the differential diagnosis. Histopathological findings of EBA include subepidermal blister formation with none or little inflammation depending on the clinical subtype. While dapsone is an effective treatment option for EED, EBA is usually refractory to many systemic agents including dapsone.

**Conclusions**

Dermal inflammation with eosinophils and fibrin deposition in histopathologic examination and dramatic response to dapsone therapy suggested the diagnosis of vesiculobullous EED rather than EBA in the current case. The present novel DIF and salt-split skin test findings expand the clinicopathological spectrum of vesiculobullous EED.

**References**

Dermatoscopic Features of a Metastatic Eccrine Porocarcinoma Arising on Lymphedema

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Key words: eccrine porocarcinoma, metastatic eccrine porocarcinoma, malignant eccrine poroma, sweat gland tumor

Citation: Sgouros D, Routsi E, Almpanis Z, Korogiannos A, Katoulis A. Dermatoscopic features of a metastatic eccrine porocarcinoma arising on lymphedema. Dermatol Pract Concept. 2022;12(2):e2022079. DOI: https://doi.org/10.5826/dpc.1202a79

Accepted: September 15, 2021; Published: April 2022

Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Eccrine porocarcinoma (EPC) is a rare type of skin cancer arising from the intraepidermal portion of eccrine sweat glands or acrosyringium and comprises of 0.005% of all malignant epithelial tumors with an equal prevalence in both sexes and a predominance of elderly patients. The reported incidence may be underestimated because EPC can also mimic clinically and dermatoscopically several other benign or malignant cutaneous tumors (eg seborrheic keratosis, Bowen disease, melanoma, etc.) typically presenting as an asymptomatic, painless and solitary nodule with ulcerated surface also developing in former sites of irradiation, lymphedema, and trauma [1,2]. EPC represents a tumor with aggressive biologic behavior and a tendency for local recurrence and regional lymph nodes metastatic potential (about 20% in both scenarios). The mortality rate of 67% in patients with lymph node metastases poses EPC as a life-threatening cutaneous neoplasm [2].

Herein we report a rare case of metastatic EPC with a zosteriform development on the right lower extremity.

Case Presentation

An 85-year-old woman, Fitzpatrick phototype IV, presented with 1-year history of multiple violaceous-black diffuse papules on the right thigh and a plaque on the mons pubis. She had no symptoms or any discharge such as pain, itch or other. Of note, the patient suffered from a stable lymphedema of unknown origin in the right lower extremity for 3 years while there was a preexisting scar on the right thigh due to a previously excised EPC 2 years ago with clear resection margins. Previous dermatological history included Bowen disease on the left leg presenting 1 year ago. Her
past medical history also included arterial hypertension and diabetes mellitus. The general examination showed no other abnormal findings. Dermoscopy revealed black coloration correlated with crusts covering areas of erosions. Structureless pink-whitish background and a lack of apparent vasculature were additional dermatoscopic findings, as well. Fine scaling surrounding sites of erosions was also evident in all lesions. Moreover, few papules exhibited pink-whitish ovoid areas. Two papules with such dermatoscopic characteristics were excised and histopathological examination showed an invasive, well-differentiated porocarcinoma with focal epidermal attachments and partial squamoid differentiation (Figure 1). Diagnostic work-up with a computed tomography revealed infiltration of homolateral inguinal lymph nodes. Concerning vascularity our findings are in contrast to published literature since EPC as well as its benign counterpart, eccrine poroma, mostly present with polymorphous vessels imitating amelanotic melanoma [1]. Our observation could be partially explained by the presence of lymphedema that might had caused suppression of vascular structures. In line with current evidence pink-whitish round areas seem to be a common finding among EPCs correlating with edematous sub-epidermal stroma reaction [2].

![Figure 1](image-url)

**Figure 1.** (A) Multiple violaceous-to-black papules coalescing into a plaque on the mons pubis. (B) Dermoscopy reveals that black coloration is associated with crusts surrounded by a structureless dark pink-to-purple background. (C) Multiple papules of a 5 mm of maximum diameter are diffusely arranged on a lymphedematous right thigh. A scar due to a former excision of an EPC can be detected on the upper external part of the extremity (black arrow). (D,E) A hint of fine scaling around areas of erosions and crusts (black arrows) and dermatoscopically evident pink-to-white ovoid structures (white arrow) can be observed. (B, D, E) Lack of apparent vasculature is also prominent in all dermatoscopic images. (F) Malignant neoplastic cells extended from the epidermis into the dermis with infiltrative growth pattern (black arrow) and were composed of large, basaloïd and atypical neoplastic cells with hyperchromatic nuclei. Depletion of vessels and lymphatic vascular ectasia due to lymphedema (red arrow) are also prominent in histological images. (G) Eccrine porocarcinoma usually composed of basaloïd cells and many times it may show squamoid features (black arrow), resembles squamous cell carcinoma, but has sweat ducts or duct-like structures (red arrow).
Conclusions

EPC represents a rare malignant cutaneous adnexal tumor with non-specific clinical and dermatoscopic features. History of previously excised EPC and lymphedema constitute risk factors for the development of metastatic cutaneous disease. Dermatoscopically observed pink-to-white ovoid structures and whitish fine scaling surrounding areas of erosions over a vague pinkish background may be of help for the early detection of this life-threatening neoplasm.

Consent: Patient has provided written consent for her data publication

References


Introduction

Verrucous epidermal nevus (VEN) is hamartoma characterized by hyperplasia of keratinocytes. Some cases of secondary tumors developing in VEN have been reported, but adnexal tumors are infrequent, especially coexistence of more than one type of adnexal tumors. We report a case of syringocystadenoma papilliferum (SCAP) and multiple eccrine poromas (EP) arising in a VEN, and the dermoscopic and ultrasonic features of these lesions.

Case Presentation

A 28-year-old woman had the band-like, light-brown verrucous plaque on her right leg since birth, with no symptoms. Four years ago, a hemispherical nodule, with erosion and bleeding recurrently, and multiple pink to violaceous papules gradually developed on the preexisting lesion.

Clinical examination revealed a band-like, light-brown plaque, extending from the middle of the right thigh to the dorsum of the right foot. On the popliteal fossa, there was a black-brown verrucous hyperplastic plaque of 10 cm in length, without erosion or exudation (Figure 1A). Skin biopsy revealed VEN.

On the right medial malleolus, there was a red nodule of 1.5 cm in diameter with erosions and yellowish crusts (Figure 1B). Dermoscopy revealed pinkish-white ulcerated areas, polymorphic vessels and yellow crusts (Figure 1C). Ultrasound showed a superficial dermal lesion with regular shape, well-defined margin and heterogeneous internal echo,
and superficial hyperechoic focus (Figure 1D). Histopathologic examination revealed endophytic tumor extended from the epidermis with intraluminal papillary fronds, which were lined by a bilayer. Dense infiltrate of lymphocytes and plasma cells and decapitation secretion could be seen (Figure 1, E and F). It was consistent with SCAP.

On the medial of the right lower leg and knee, there were 3 pink to violaceous papules (Figure 2, A and B). Under dermoscopy, white streaks, short linear, coiled and looped vessels with yellow background were observed (Figure 2C). Ultrasound showed well-defined, oval-shaped dermal lesions with heterogeneous internal echo and hyperechoic spots (Figure 2D). These papules had a similar appearance under microscopy. Well-circumscribed dermal neoplasms continuous with the epidermis. Ductal differentiation was noted (Figure 2, E and F). The diagnosis of EP was made.

The tumors were resected and the patient was still under follow-up.

Discussion

VEN derive from hyperplasia of keratinocytes, unlike organoid epidermal nevi, secondary tumor is relatively infrequent, and most of them are epithelial tumors [1,2]. However, SCAP and EP are both benign adnexal neoplasms, which are quite rare in VEN. To the best of our knowledge, the case of SCAP and EP successively developed in a VEN has not been documented previously.

We applied non-invasive skin imaging techniques in the diagnosis. We observed the dermoscopic feature of polymorphous vascular pattern, a sign of malignancy. It indicated a biopsy should be performed. The ultrasound showed the lesions were in the superficial dermal with well-defined margin, which indicated that they tended to be benign conditions and helped assess the excision extension.

Conclusions

We reported a quite rare case of SCAP and EP arising in a VEN. We applied dermoscopy and high-frequency ultrasound in the evaluation, and demonstrated the multidimensional skin imaging features of SCAP and EP.
Figure 2. (A,B) Clinical presentation: 2 violaceous papules on the medial of the right knee, and one pink papule on the lower leg (black arrows). (C) Dermoscopy showed white streaks, short linear, coiled and looped vessels, with yellow background. (D) Ultrasound revealed a well-defined, oval-shaped dermal lesion with heterogeneous internal echo and hyperechoic spots (50 MHz). (E) Epitheliomatous hyperplasia of the epidermis, well-circumscribed dermal neoplasms continuous with the epidermis. Inflammatory cells infiltrated in the superficial dermis (H&E staining; original magnification, ×40). (F) Ductal differentiation was noted (H&E staining; original magnification, ×100).

References


Introduction

Psoriasis and multiple sclerosis (MS) are both autoimmune T-cell mediated diseases that share a possible common genetic linkage [1]. Natalizumab is a recombinant humanized monoclonal antibody targeting the cell adhesion molecule α4 integrin and is labeled to treat MS. It is known that biological agents induce cutaneous adverse drug reactions. Although there is not a defined link between natalizumab and psoriasis, there are case reports describing a possible relationship [2]. Here, we report on a patient with MS who developed pustular psoriasis of palms and soles after natalizumab treatment.

Case Presentation

A 50-year-old woman presented with multiple millimetric pustules and scaling sites on erythematous plaques on the palms and soles (Figure 1A). Personal and familiar history for psoriasis was negative. She has been treated with natalizumab for 6 months for MS. Dermoscopy revealed yellow globules and crusts along with the dotted vessels (Figure 1B). The patient was diagnosed with pustular psoriasis of palms and soles.

Discussion

Data on whether natalizumab can induce or aggravate psoriasis are limited. In literature, 2 of the cases developed plaque psoriasis while 1 patient had new-onset psoriatic arthritis during natalizumab treatment. Family history of psoriasis was positive in all patients. One patient affected by mild psoriasis had a severe flare-up after several natalizumab infusions [2]. Our patient, on the other hand, differs from those cases due to the absence of family history and the development of localized pustular psoriasis.

Although there are pieces of evidence showing common pathophysiological pathways in psoriasis and MS, it has been observed that treatment of one condition did not provide a parallel improvement in the other one. T helper 17 (Th17) cells are involved in the inflammation stage of both disease [1]. The pathophysiological mechanism between
psoriasis and natalizumab remains unclear but natalizumab has been associated with paradoxical activation of autoimmune disorders by pathologically stimulating the production of IL17 and increased activation of Th17 cells [2].

**Conclusions**

We highlight that a new onset of palmoplantar pustular psoriasis may also be a rare side effect of natalizumab. There is not enough data yet to make a recommendation regarding the consideration of psoriasis history in the patient or in the family when deciding for natalizumab treatment. More research is needed to understand the relationship between natalizumab and psoriasis.

**References**

Dermoscopic Features of Amelanotic and Hypomelanotic Melanomas: a Review of 49 Cases

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Key words: Hypomelanotic melanoma, amelanotic melanoma, dermoscopy, dermatoscopy, skin cancer

Citation: Dawood S, Altayeb A, Atwan A, Mills C. Dermoscopic features of Amelanotic and Hypomelanotic Melanomas: A review of 49 cases. Dermatol Pract Concept. 2022;12(2):e2022060. DOI: https://doi.org/10.5826/dpc.1202a60

Accepted: October 21, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction

Amelanotic and hypomelanotic melanomas (AHM) represent 2-8% of all melanomas. They are often diagnosed late due to the lack of a distinctive clinical appearance. As a result, AHM is associated with higher mortality compared with pigmented melanomas. It is, therefore, crucial to be aware of the dermoscopic features of such lesions to aid early diagnosis.

Case Presentation

During a 6-year period (2014-2019), a total of 165 melanoma cases were diagnosed via our teledermoscopy service, using Nikon D300S camera and Heine® Delta 20T dermatoscope. Of those, 49 cases (29.7%) were AHM, including 27 males and 22 females with a median age of 68 years (range 16-87 years). Most AMH were on the upper limbs (20 patients) and the trunk (13 patients). The rest were on the lower limbs (9 patients), and head and neck (7 patients).

Most lesions (n = 46, 83.8%) were invasive AHM (superficial spreading = 27; nodular = 14; desmoplastic melanoma = 3; lentigomaligna melanoma = 2). The remaining 3 lesions were in situ AHM. The median Breslow thickness of AHM was higher than pigmented MM (AHM = 1.7 mm interquartile range [IQR] = 3.50) versus 0.98 mm (IQR = 1.23) for pigmented MM).

Short white lines (Figure 1B) and milky-red areas (Figure 2B) were the most common dermoscopic findings in our cohort of AHM, observed in 39 lesions (79.6%) and 33 lesions (67.3%), respectively. Milky-red areas were present in similar frequencies in lesions ≤ 1 mm in thickness (70%) and lesions > 1 mm in thickness (63.9%) (Table 1).

In our study, 63.3% of AHM had more than one vascular pattern (Table 1). Dotted, linear, and looped vessels were present in 57.1%, 63.2%, and 63.3% of lesions, respectively. Dotted vessels were seen in 90% of AHM of < 1mm, compared with 44.4% of AHM of > 1mm.

Remnant pigment was present in 27 lesions (55.1%), and present in 70% of lesions ≤ 1mm in thickness and 50% of lesions > 1 mm in thickness. Gray granular structures and lacunae were less frequently seen, found in 44.9% and 26.5% of lesions, respectively.
Discussion

Short white lines were the most common finding in our cohort, seen in 79.6% of cases. This is higher than reported observations at 30.8% [1]. We assume reviewing magnified images on the monitor contributed to better visualization of these subtle features.

The incidence of milky-red areas in our study (67.3%) was close to the incidence reported in the literature at 54.5% [2,3]. Also, polymorphic vessels, an important distinguishing feature in AHM, were present in over 50% of our AHM cases.

Dotted vessels were present in nearly half of our cases. This was similar to the incident reported in the literature [1]. Zalaudeket al reported a strong association between

Figure 1. (A) Lesion on the forearm of a 46-year-old woman. A confirmed melanoma with Breslow thickness of 1.1 mm. (B) Dermoscopy shows dotted (black arrows) and looped (white arrows) vessels, milky red areas (stars), and white structures (long arrows).

Figure 2. (A) Lesion on the lower leg of a 57-year-old woman. A confirmed melanoma with Breslow thickness of 3 mm. (B) Dermoscopy shows irregularly distributed dotted vessels (arrows), a milky red area (star), and a subtle remnant of pigment at the periphery.
dotted vessels and AHM with Breslow thickness less than 1 mm [4]. Our study supports this observation.

Conclusions

Our study reinforces the findings that polymorphic vessels and milky-red areas are common features of AHM. In addition, our study indicates that short white lines are also common and helpful predictive feature. Clinicians should be aware of these dermoscopic findings when non-specific lesions are encountered.

Acknowledgement

We thank the Medical Illustration Department at Aneurin Bevan University Health Board for providing the teledermatology service.

References

Case Presentation

A 66-year-old male presented with pigmented lesions that he had for a few months. Diagnosis of erythema dyschromicum perstans was made based on clinical appearance (asymptomatic, blue-grayish patches of varying sizes, some with erythematos borders, distributed on the face, arms, shoulders and trunk) (Figure 1 A-D), histopathology (atrophic epidermis, superficial and perivascular lymphocytic infiltrate and pigment incontinence in the dermis) (Figure 1E) and dermoscopy (gray-bluish small dots over a bluish base) (Figure 1F).

Teaching points

In everyday practice and for every skin lesion, the use of dermoscopy as a supportive tool is highly recommended. In a case of erythema dyschromicum perstans (EDP), there are significant clinical, histological and dermoscopic similarities between EDP and other acquired dermal macular hyperpigmentations-pigmented contact dermatitis and lichen planus pigmentosus [1]. Viney et al reported that severity of pigmentation by dermoscopy is comparable with severity of clinical and histological findings but there are no specific dermoscopic differences to differentiate these diseases [1,2]. Four dermoscopic grades were observed: 1) discrete pigment dots without any pattern; 2) pigment dots and globules arranged in broken net pattern; 3) pigment dots and globules in a well-formed net-like pattern and 4) diffuse pigment dots, globules and blotches, sparing only gland openings [1]. According to the given classification, first grade corresponds to our case. Presence of dots, globules and blotches in EDP differs from other hyperpigmentations, such as melasma where pseudo- reticular network is observed or in the case of nevus Ota where slate-gray structureless areas are present [1].
References


Figure 1. (A-D). Blue-grayish patches of varying sizes, some with erythematous borders localized on the face, arms, shoulders and trunk. (E) Atrophic epidermis, superficial and perivascular lymphocytic infiltrate and pigment incontinence in the dermis (H&E x100). (F) Dermoscopic image: gray-bluish small dots over a bluish base (Dermatoscope Heine Delta 20 Led Plus).
Childhood Flexural Comedones

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Citation: Zhang L, Wu J, Zheng L, Chen T. Childhood flexural comedones. Dermatol Pract Concept. 2022;12(2):e2022053. DOI: https://doi.org/10.5826/dpc.1202a53
Accepted: August 14, 2021; Published: April 2022
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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 20-year-old female complained of an asymptomatic papule on the left postauricular skin that occurred shortly after birth. The lesion presented a single papule with double-orifice comedones (Figure 1A). At the same site, previous skin lesion or inflammation were not observed. The dermoscopy manifested double-ended pseudo-comedones (Figure 1B).

Childhood flexural comedones (CFC) with late diagnosis in adulthood was established.

Teaching Point

CFC usually occur in the skin folds including axilla, neck, cubital fossa, and perineum, and present as double opening comedones connected by a thin layer of the epidermis.

Figure 1. (A) A single papule with double-orifice comedones on the left postauricular skin. (B) The dermoscopy manifested double-ended pseudo-comedon.
The etiology hypotheses included potential precursors of hidradenitis suppurativa, friction, genetic background, and hamartomatous origin [1]. Histopathology showed typical open comedo with follicular plugging and infundibular dilatation [2]. Three different dermoscopic patterns of CFC have been described including cuneiform comedo, multi-orifice comedo, and double-ended pseudo-comedones [1]. The differential diagnosis includes other diseases associated with comedones, such as nevus comedonicus, acne neonatorum, familial dyskeratotic comedones, and idiopathic disseminated comedones.

References
Dermoscopy to the Rescue in an Annular Enigma: A Rare Case of Annular Pityriasis Versicolor Presenting in an Unusual Location

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Citation: Kapadia F, Kharkar V, Vishwanath T. Dermoscopy to the Rescue in an Annular Enigma: A Rare Case of Annular Pityriasis Versicolor Presenting in an Unusual Location. Dermatol Pract Concept. 2022;12(2):e2022057. DOI: https://doi.org/10.5826/dpc.1202a57

Accepted: August 22, 2021; Published: April 2022

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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 29-year-old female presented with asymptomatic annular plaques solely over the medial thighs since 1 month (figure 1A, inset, 1B). Considering annular lichen planus and porokeratosis, dermoscopy (polarized, Otiez dermoscope) was performed. It revealed attenuated central pigmented network and white scales and peripheral brown peripheral scales with accentuation in skin creases (Figure 1C). Scales disappeared after wiping with spirit swab (Figure 1D). On Woods lamp examination- yellowish fluorescence was seen (Figure 1E). On potassium hydroxide mount with Chicago Sky Blue, hyphae and spores were evident (Figure 1F). Thus, a diagnosis of pityriasis versicolor was made.

Teaching Point

Pityriasis versicolor presents with varied color tones and morphologies.1,2 The annular variant noted in the present case has not yet been described. Therefore, the diagnosis was not clinically suspected. Dermoscopy was the game changer since it gave telltale clues: scales in skin creases along with pigment dilution. Peripheral brown scales without accentuation in the creases constitute an unusual feature probably due to retention parakeratosis since it disappeared on swabbing.
Figure 1. (A,B) Multiple discrete scaly annular patches with peripheral rim of hyperpigmentation and central hypopigmentation over bilateral thighs. (C) Dermoscopy (captured with polarized dermoscopy, magnification x 10) revealed brown scales at the periphery of the lesion with white fine scales at the center within the skin creases. (D) On wiping the lesion with an alcohol swab, dermoscopic analysis showed complete disappearance of brown scales in the periphery with pigment dilution in the center. (E) Yellowish green fluorescence seen at Woods lamp examination (F) KOH mount shows fungal spores and hyphae (spaghetti and meatball appearance).
References


Card Test as a Simple Method to Diagnose Short Anagen Syndrome

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Citation: Iorizzo M, Starace M. Card Test As a Simple Method to Diagnose Short Anagen Syndrome. Dermatol Pract Concept. 2022;12(2):e2022059. DOI: https://doi.org/10.5826/dpc.1202a59

Accepted: August 19, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: Both authors have contributed significantly to this publication.

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Case Presentation

In short, anagen hair syndrome (SAS), the hairs are short, fine, and sparse since birth even if the typical patient presents to a medical consultation around the age of 5-6 years. Parents often complain the hair doesn't grow long and that they have never been cut. The presence of short hair shafts is due to a short duration of the anagen phase. Hair shafts have also been described as thinner and in telogen phase. The clinician should rule out congenital hypotrichosis, loose anagen hair syndrome, telogen effluvium.

Teaching Point

We propose the card test as a quick and inexpensive method to help in the diagnosis of SAS. Tufts of hairs are placed on a card (Figure 1A) and observed with a dermoscope at 20X magnification: thin hair shafts with pointed tips are proof the hairs have never been cut (Figure 1B). This test can be done even without pulling the hair out of the scalp.

Figure 1. (A) The card test showing how a tuft of short hairs should be placed on a card before observing them with a dermoscope. (B) Multiple and exclusively pointed tips, showing the short shafts have never been cut, and after cut, are easily seen with a 20X magnification.
Supine Dermoscopy for Improved Visualisation of Lower Limb Lesions

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Accepted: August 19, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication

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Case Presentation

Dermoscopic evaluation of suspicious lesions in the context of venous insufficiency, such as varicose veins, venous stasis, and lipodermatosclerosis, remains a diagnostic challenge. The background erythema created by non-lesional vasculature often obscures the assessment of true lesional structures.

Teaching Point

Dermoscopy helps assess for atypical vascular morphology such as predominantly central vessels, polymorphous vessels, and milky red-pink areas, which is critical in differentiating malignant from benign pigmented skin lesions, especially in the context of amelanotic and hypomelanotic melanoma [1,2].

To better delineate skin lesion vasculature from background vascular noise, consider laying patients supine to reduce venous congestion (Figure 1). This is particularly important in gravity-dependent areas such as the lower limbs. Furthermore, use non-contact polarized dermatoscopes or immersion fluids of a high viscosity with contact dermatoscopes, to minimize blanching of vessels and thereby maximizing visualization of vascular architecture in cutaneous lesions [1].

References

Figure 1. (A,C,E) Dermoscopy of cutaneous lesions of the lower leg with patients standing up. Minimal pressure was applied. Note the prominent background blood vessels which may obscure proper examination of the skin lesion of interest. (B,D,F) Dermoscopy of the same lower leg skin lesions with patients laying supine. Minimal pressure was applied. Reduced background blood vessels allow for clearer visualization of the lesion. Dermoscopic pictures taken with Medicam 1000, FotoFinder Systems.
Intralymphatic Histiocytosis

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Case Presentation

An 87-year-old man presented to our Dermatology department with a history of 1-year-long asymptomatic erythematous plaques on his left shoulder. He referred he had been previously diagnosed from severe osteoarthritis on this location. Moreover, he denied taking regular medication, exposure to heat or suffering from any other medical condition.

Dermatological examination showed 2 mm wide serpiginous erythematous plaques with a vascular anatomic distribution on the anterior side of his left shoulder (Figure 1). Neither cervical nor axillary adenopathies were detected. After taking a punch-biopsy, a diagnosis of intralymphatic histiocytosis was established.

Teaching point

Intralymphatic histiocytosis is a benign proliferation of histiocytes within lymphatic vessels [1]. Although its etiopathogenesis has not yet been clearly elucidated, it has been associated to several chronic inflammatory and degenerative disorders, such as osteoarthritis [2]. Thus, Dermatologists should take into account this entity whenever they are facing serpiginous erythematous plaques with a vascular distribution on a persistent swollen joint.

Figure 1. 2 mm wide serpiginous erythematous plaques with a vascular distribution on the left shoulder.
References


Milium of the Nipple

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Citation: Zhang L, Wu J, Zhao L, Chen T. Milium of the Nipple. Dermatol Pract Concept. 2022;12(2):e2022086. DOI: https://doi.org/10.5826/dpc.1202a86

Accepted: October 7, 2021; Published: April 2022

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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 4-year-old boy presented with a 1-year history of a single pearly white papule on the right nipple (Figure 1A). No previous skin inflammation or trauma was observed at the same location. The left nipple was normal. His growth and psychomotor development were normal. The dermoscopy showed a pearly white rounded structure with branching vessels (Figure 1B). Histopathology showed an epidermoid cyst containing keratinous material (Figure 1C). The diagnosis of milium was made.

Teaching Point

Milium is a common benign keratinous cyst characterized by pearly white dome-shaped lesion of 1 mm to 4 mm in diameter, but the involvement of the nipple seems to be rare and bigger. Milium may occur as either primary or secondary lesions. Four cases of milium involving the nipple were found by searching PubMed databases [1,2]. Among them, the male-to-female ratio was 1:3; the age range was from 6 to 16 months. They presented a unilateral single pearly white dome-shaped papule with a diameter of 3 mm to 8 mm. Three cases underwent surgical excision, and 1 spontaneously disappeared. The dermoscopic manifestation shows a white or yellowish-white rounded structure with linear or branching vessels. The differential diagnosis includes molluscum contagiosum, calcinosis cutis, juvenile xanthogranuloma, and syringoma.

References

Figure 1. (A) A single pearly white papule on the right nipple. (B) The dermoscopy showed a pearly white rounded structure with branching vessels. (C) Histopathology showed an epidermoid cyst containing keratinous material (H&E; ×100 magnification)
Dotted Vessels in a Reticular Arrangement

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Citation: Delli FS, Noukari D, Apalla Z, Lallas A. Dotted vessels in a reticular arrangement. Dermatol Pract Concept. 2022;12(2):e2022089. DOI: https://doi.org/10.5826/dpc.1202a89
Accepted: September 26, 2021; Published: April 2022
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Competing interests: None.
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Case presentation

We report a case of a 56-year-old male patient who presented for evaluation of a tumor on his right lower back (Figure 1A). He reported that he observed the lesion for the first time 3 years earlier and, since then, it gradually increased in size and was sporadically traumatized.

Dermoscopy revealed glomerular and dotted vessels with a reticular arrangement at the periphery of the lesion (white circles, Figure 1B), but also linear mixed and hairpin-like vessels (white arrows, Figure 1B) irregularly distributed in the center and eccentrically. White structureless areas were also focally present (Figure 1B).

Although retically arranged dotted vessels are suggestive of a clear cell acanthoma (CCA) (1), the uneven distribution of vessels in the lesion and the co-existence of other morphologic vessel types did not allow a confident clinical diagnosis. Therefore, the lesion was excised with a clinical differential diagnosis including CCA, non-pigmented eccrine poroma (2), amelanotic melanoma and poorly differentiated squamous cell carcinoma.

Histopathology confirmed the diagnosis of CCA.

Teaching Point

Dotted vessels in a reticular arrangement (“string of pearls” in the metaphoric terminology) are strongly indicative of CCA.

However, excisional biopsy and histopathological examination is mandatory for any nodular lesions that will express only in part the dermoscopic criteria for clear cell acanthoma.

References


Figure 1. (A) Nodular and pink skin lesion measuring 23 mm on patient right lower back. (B) Glomerular and dotted vessels with a reticular arrangement at the periphery of the lesion (white circles), linear mixed and hairpin-like vessels (white arrows irregularly distributed in the center and eccentrically. White structureless areas were also focally present.
Case presentation
An 80-year-old man was referred for a new eyelid papule in proximity of a scar from a previously excised basal cell carcinoma (BCC) (Figure 1). Based on naked-eye examination, recurrent BCC was suspected, and surgery was performed. The histopathological features were consistent with apocrine hidrocystoma (AH).

Teaching point
AH is a benign cystic lesion of the apocrine glands usually found on the head and neck, particularly periorcular [1]. When arising in or around scars of patients with previous BCC, diagnosis becomes challenging. Dermoscopy might be a helpful tool. Our patient prior BCC showed eyelash destruction, in-focus arborizing telangiectasias and blotches and strands on dermoscopy (Figure 1, A and B) [2]. AH, on the other hand, was clinically similar but on dermoscopy it had translucent homogenous areas, linear whitish structures, and no eyelash involvement, as previously reported in literature (Figure 1, B-F) [1,2]. Dermoscopy might help differentiate recurrent BCC from other adnexal tumors, potentially avoiding unnecessary procedures.
References


Figure 1. A 80-year-old man referred for a new eyelid papule in proximity of a scar from a previously excised basal cell carcinoma. (A) Pearly papule with eyelash destruction. Histopathology confirmed a basal cell carcinoma. (B) Dermoscopy showing eyelash destruction, in-focus arborising telangiectasias, and blotches and strands (polarized dermoscopy, x10). (C) Homogeneous skin colored papule near previous scar. Histopathology confirmed an apocrine hidrocystoma. (D) Dermoscopy showing no eyelash involvement and linear whitish structures (polarized dermoscopy, x10). (E) Dermoscopy showing translucent homogenous area and no eyelash involvement (non-polarized dermoscopy, x10). (F) Surgery of the new eyelid papule. Histopathology confirmed an apocrine hidrocystoma.
Case Presentation

A 9-year-old boy presented with a 4-month history of chronic nodular lesion on the cheek resistant to antibiotics. Dermatological examination showed a 15-mm, solitary, firm erythematous nodule on his right cheek (Figure 1a). A punch biopsy specimen revealed a dermal chronic inflammatory, granulomatous perifollicular infiltrate consisting of histiocytes, neutrophils, and giant cells without necrosis (Figure 1: b, c). Based on these findings, we diagnosed the case as idiopathic facial aseptic granuloma (IFAG).

Teaching Point

IFAG is a rare, benign pediatric entity characterized by chronic, painless erythematous-violaceous nodular lesions frequently located on cheeks and eyelids with no predisposing factor [1]. Although pathogenesis remains unclear, the disease is thought to be associated with granulomatous rosacea in childhood [1]. Histologically, IFAG lesion is characterized by a dermal chronic inflammation of histiocytic granuloma with giant cells, and abscesses without necrosis. In general, IFAG tends to resolve spontaneously in less than a year. Antibiotics, such as doxycycline and metronidazole, could be used to accelerate the involution of IFAG [2].
Figure 1. (A): Solitary, Firm, nodular, erythematous lesion on the right cheek, chronic granulomatous inflammatory infiltrate in the dermis (B, HE*40) composed of histiocytes, lymphocytes, neutrophils and giant cells without necrosis (C, HE*200).

References


A 13-year-old female patient was referred to our department for a thoracic lesion present since birth. The physical examination reveals grouped vesicles with clear and hematic content similar to “frog roe”, with a subcutaneous component and a zosteriform distribution (Figure 1A). She referred episodes of pain and increased soft tissue associated for a few months ago. The polarized light dermoscopy showed pink lacunae divided by white septa and polymorphic vessels. Besides, the “hypopyon sign” was shown inside the lacunae (Figure 1B). The magnetic resonance imaging study reported mixed veno-lymphatic vascular malformation.

“Hypopyon sign” is referred to the 2 shades of colors inside the lacunae (corresponding to dilated, thin-walled lymphatic vessels located in the papillary dermis) due to the blood deposited at the lower side of them, due to the gravity effect, and it is a well described finding in circumscribed lymphangioma [1,2]. Nevertheless, it is useful for the diagnosis of any vascular malformation with lymphatic component, as show in our case.

Teaching point


Accepted: July 23, 2021; Published: April 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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References


Figure 1. (A) Clinical presentation as grouped vesicles with clear and hematic content similar to “frog roe” with a zosteriform distribution. (B) Dermoscopy (polarised, 25x) of reddish lesions showing half-and-half lacunae demonstrating hypopyon-like features.