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Serum Copper and Zinc Levels Among Iranian Vitiligo Patients

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ABSTRACT

Introduction: Vitiligo is a chronic skin disease, which its etiopathogenesis is not fully understood. Numerous studies have suggested that oxidative stress may play a role in the pathophysiology of vitiligo. There are controversial reports as to the changes of serum trace elements, copper (Cu) and zinc (Zn) levels in vitiligo patients.

Objectives: We evaluated the alterations in the level of serum Cu and Zn among a group of Iranian vitiligo patients.

Methods: The levels of serum Cu and Zn were compared between 117 vitiligo patients and 137 healthy controls using atomic absorption spectrophotometry.

Results: The mean Cu and Zn levels in the cases (113.57 ± 59.43 and 95.01 ± 58.95 μg/dl, respectively) were significantly lower than those of the controls (138.90 ± 38.14 and 121.83 ± 33.80 μg/dl, respectively) (P = 0.00). We also observed significantly lower serum Cu and Zn concentrations in young (< 50 years) than the elderly (≥ 50 years) patients (P = 0.00). The mean Cu and Zn levels in the patients with generalized vitiligo (111.63±54.18 and 93.11±59.33 μg/dl, respectively) were significantly lower than patients with localized vitiligo (120.74±71.64 and 98.69±58.63 μg/dl, respectively) and those in the control (P = 0.00). The serum Cu/Zn ratio obtained in the young and male patients was higher than those in their matched controls (P = 0.01).

Conclusions: The current study has shown that the disturbance of serum Cu and Zn levels is associated with vitiligo, and may play an important role in the disease development of Iranian patients.
Introduction

Vitiligo is a multifactorial hypo-melanotic disorder characterized by the appearance of white spots of different sizes and shapes on the skin. The disease affects 0.1% to 8.8% of the world's population, with a higher prevalence among pigmented racial groups [1,2]. The loss of functional melanocytes has been detected histochemically in the skin as well mucous membranes, hair, and the retina of vitiligo patients [3]. Many different factors, including genetics, oxidative stress, environment, metabolic abnormalities, autoimmunity mediated by autoreactive CD8+ T lymphocytes, and interferon-γ CXCL10 cytokine signaling pathway may be involved in the pathogenesis of the disease [4-6]. The exact mechanisms and interactions of these factors in the etiology of vitiligo are unclear. Previous studies have suggested that oxidant/antioxidant imbalance and oxidative stress may also play important roles in the pathogenesis of vitiligo [7,8]. Antioxidant deficiency and the accumulation of reactive oxygen species in the epidermal lesions of vitiligo patients have been also reported. Epidermal lesions of vitiliginous skin show decreased catalase activity and increased H2O2 and nitric oxide levels [8,9]. Previous studies have indicated that both localized and generalized vitiligo were associated with low total antioxidant and high total oxidant status, as compared with healthy controls [10].

Oxidative stress inhibits melanin production by interfering with tyrosinase activity in the epidermis, thereby exerting the cytotoxicity of melanocytes [11]. Melanin, a dark biopigment found in the skin has a high affinity for binding and sequestering zinc, copper, and other metal ions [12]. Zn and Cu trace elements are required as cofactors by tyrosinase, and many other metalloenzymes involved in melanin biogenesis [13,14]. They are also essential cofactors for the activity of superoxide dismutase, an antioxidant enzyme that protects skin against reactive oxygen species [15]. Although these trace elements are essential for human health, the imbalance of the Cu/Zn ratio suggested being associated with many human diseases [16,17]. Zinc may play a role in the etiology of vitiligo through Zn-α2-Glycoprotein (ZAG), a major plasma protein involved in melanocyte growth and differentiation. Studies have shown that ZAG deficiency is involved in the pathogenesis of vitiligo through the shedding and loss of melanocytes [18]. The relationship between changes in the levels of Cu and Zn trace elements in tissues or serum and the pathogenesis of vitiligo is controversial. Some studies have shown that oral supplementation or topical treatment of Cu and Zn may improve the clinical symptoms of vitiligo [19,20]. Both increased and decreased serum levels of these trace elements in vitiligo patients have been reported [19,21-23]. In a study of 50 Sudanese vitiligo patients, a significant increase in the mean serum concentration of Cu level was observed [24]. It has been suggested that melanocytes degeneration and lower melanin biosynthesis in vitiligo patients may result in increased serum Cu and Zn levels. Hence, the high serum levels of these elements in vitiligo are the result of the disease rather than its underlying cause [25]. Several other studies have reported significantly decreased serum levels of Cu and/or Zn among vitiligo patients [21,26-29].

Objectives

In view of this controversy, the purpose of the present study was to investigate the changes in serum Cu and Zn concentrations among Iranian vitiligo patients.

Methods

Experiment Groups

One hundred and seventeen sera were obtained from the previously collected serum samples of vitiligo patients (48 men and 69 women) from the biobank of the Autoimmune Diseases Research Center of Shiraz University of Medical Sciences (SUMS). The control group consisted of 137 healthy blood donors (62 males and 75 females) with no signs of skin or systemic disease. According to the dermatology and Wood lamp examination, 84% of patients had generalized/universal and 16% of localized/segmental stable vitiligo. The University ethics committee approved the protocol for this study (Approval Number: IR.SUMS.REC.1398.629), and the informed consent was obtained from all study participants.

Preparation of the Samples and Analytical Methods

The methods for the preparation of samples and their analysis have been described previously [16]. Briefly, blood samples were collected from participants, and allowed to clot, and serum was separated and stored in plastic tubes at -80 °C until analysis. The concentrations of Cu and Zn in the samples were measured using a flame atomic absorption spectrometer (PerkinElmer model analyst 300). Stock standard solutions of Zn and Cu were prepared by 1:1 dilution of either trace element (Merck) solutions (2 mg/ml in HCl) with deionized water. The stock solutions of Zn or Cu were diluted with glycerol (5% or 10%, respectively) and used as working solutions to calibrate the instrument. The absorbance of Cu and Zn was read at 324.7 and 213.9 nm, respectively. The concentrations of trace elements in samples were calculated using PerkinElmer AA WinLab software.

Statistical Analysis

The statistical analyses of data were performed using the SPSS software package (version 16; SPSS Inc.). The results were
expressed as mean ± standard deviation (SD). Differences between cases and controls were tested by Kruskal–Wallis test, and the influence of sex and age on the serum levels of trace elements was evaluated using the Mann–Whitney U-test. The Spearman rank correlation test was used to analyze the correlation between quantitative variables. A P equal or lower than 0.05 was considered statistically significant.

Results

A total of 117 subjects with vitiligo and 137 healthy volunteers were included in this study. Tables 1 and 2 show the demographic characteristics and serum levels of Cu and Zn in patients with vitiligo and the control group. Ninety-seven patients had generalized vitiligo and 20 had localized vitiligo (Table 2). The skin phototypes were type III (70%) and type IV (30%). The duration of the disease ranged from 1-11 years, with a mean of 9.57± 9.25 years.

In this study, the serum Cu level in patients ranged from 6.11 to 289.36 μg/dl (mean: 113.57 ± 59.43 μg/dl) and that for the control group was 71.21 to 231 μg/dl (mean: 138.90 ± 38.14 μg/dl). Serum zinc concentrations in patients with vitiligo ranged from 6.15 to 273 μg/dl (mean: 95.01 ± 58.95 μg/dl) and that for the control group was 32.64 to 190.20 μg/dl (mean: 121.83 ± 33.80 μg/dl). Statistical analysis showed that compared with healthy controls, there were significant differences in serum copper and zinc levels in patients with vitiligo (P = 0.00) (Table 1).

The age of patients ranged from 19 to 66 years old (Mean: 37.64 ± 13.01 years) and that of control 26 to 60 years old (Mean: 47.19 ± 8.03 years). In terms of the prevalence of disease, the highest rate was in the 25 to 28 year age group (17%). The median age of vitiligo patients was about 34 years. Since the serum levels of Zn and Cu have been reported to increase by age [30], we divided the subjects into two groups of young (< 50 years) and old (≥ 50 years) groups. We found significantly lower serum Cu and Zn concentration among young patients (107.12 ± 61.18 and 82.47 ± 47.40 μg/dl, respectively) than the elderly group (122.53 ± 56.30 and 114.37 ± 67.27 μg/dl, respectively) (P =0.00) (Table 1). In the case-control comparison of two age groups, we found that the serum copper concentrations of cases were lower than those in the respective control group (P ≤ 0.05). The mean serum Zn levels of young cases were also lower than the corresponding value in the respective controls (P = 0.00) while there was no significant difference between the mean serum Zn concentrations of the elderly subjects and controls (P = 0.535). Although, in the case-case comparison of two age groups, a higher Cu/Zn ratio was found in the young cases than elderly patients (1.96 ± 2.09 vs 1.64 ± 1.67), the difference didn't reach the level of significance (P = 0.406). There was no significant difference in serum copper and zinc levels between

### Table 1. Serum copper and zinc levels among vitiligo patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Cu (μg/dl Median)</th>
<th>Cu (μg/dl Mean ± SD)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cu (μg/dl Median)</th>
<th>Cu (μg/dl Mean ± SD)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Zn (μg/dl Median)</th>
<th>Zn (μg/dl Mean ± SD)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Zn (μg/dl Median)</th>
<th>Zn (μg/dl Mean ± SD)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
<th>[Cu]/[Zn]</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>Cases (N)</td>
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<tr>
<td>Total (117)</td>
<td>103.41</td>
<td>113.57 ± 59.43</td>
<td>0.000</td>
<td>76.17</td>
<td>95.01 ± 58.95</td>
<td>0.000</td>
<td>1.81 ± 1.90</td>
<td>0.488</td>
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<td>&lt;50 Y (68)</td>
<td>107.12 ± 61.18</td>
<td>114.65 ± 56.30</td>
<td>0.000</td>
<td>72.01</td>
<td>82.47 ± 47.40</td>
<td>0.000</td>
<td>1.96 ± 2.09</td>
<td>0.018</td>
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<td>≥50 Y (49)</td>
<td>122.53 ± 56.30</td>
<td>138.90 ± 38.14</td>
<td>0.050</td>
<td>101.06</td>
<td>114.37 ± 67.27</td>
<td>0.535</td>
<td>1.64 ± 1.67</td>
<td>0.161</td>
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<tr>
<td>Male (48)</td>
<td>110.68</td>
<td>114.65 ± 63.88</td>
<td>0.015</td>
<td>76.34</td>
<td>99.12 ± 62.10</td>
<td>0.000</td>
<td>1.67 ± 1.48</td>
<td>0.011</td>
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<td>Female (69)</td>
<td>108.94</td>
<td>112.95 ± 56.32</td>
<td>0.000</td>
<td>75.09</td>
<td>92.25 ± 56.83</td>
<td>0.000</td>
<td>1.90 ± 2.15</td>
<td>0.087</td>
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<td>Controls, (N)</td>
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<tr>
<td>Total (137)</td>
<td>138.58</td>
<td>138.90 ± 38.14</td>
<td>0.000</td>
<td>118.42</td>
<td>121.83 ± 33.80</td>
<td>0.000</td>
<td>1.28 ± 0.56</td>
<td>0.000</td>
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<tr>
<td>&lt;50 Y (71)</td>
<td>143.82 ± 30.73</td>
<td>143.82 ± 30.73</td>
<td>0.338</td>
<td>122.14</td>
<td>124.80 ± 33.05</td>
<td>0.321</td>
<td>1.24 ± 0.43</td>
<td>0.001</td>
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<tr>
<td>≥50 Y (66)</td>
<td>138.74</td>
<td>138.70 ± 31.59</td>
<td>0.113</td>
<td>117.02</td>
<td>118.84 ± 34.59</td>
<td>0.321</td>
<td>1.32 ± 0.66</td>
<td>0.008</td>
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<tr>
<td>Male (62)</td>
<td>137.08</td>
<td>135.46 ± 25.13</td>
<td>0.044</td>
<td>126.10</td>
<td>126.87 ± 29.28</td>
<td>0.113</td>
<td>1.14 ± 0.3</td>
<td>0.000</td>
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<tr>
<td>Female (75)</td>
<td>142.38</td>
<td>146.22 ± 34.76</td>
<td>0.044</td>
<td>111.40</td>
<td>112.53 ± 33.78</td>
<td>0.000</td>
<td>1.39 ± 0.69</td>
<td>0.000</td>
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Cu = copper; SD = standard deviation; Y = years; Zn = zinc.

<sup>a</sup> values for case–control comparisons from Kruskal–Wallis or Mann–Whitney U test where appropriate

<sup>b</sup> values for case–case or control-control comparisons from Kruskal–Wallis or Mann–Whitney U test where appropriate
male and female patients. However, in male and female cases, the average serum copper and zinc levels were significantly lower than their matched control group (P < 0.02) (Table 1). The patients with generalized vitiligo had significantly lower serum Cu levels (111.63±54.18 μg/dl) than patients with localized vitiligo (120.74±71.64 μg/dl) (P = 0.04) and healthy controls (138.98±28.12 μg/dl) (P = 0.00). The mean serum Zn level of the patients with the generalized vitiligo (93.11±59.33 μg/dl) also differed significantly with those with the localized vitiligo (98.69±58.63 μg/dl) and the control group (P = 0.00). We found significantly lower serum Zn, but higher Cu/Zn ratio in patients with skin type IV (86.16±60.62 μg/dl and 2.45±2.75, respectively) than in patients with skin type III (99.24±59.91 μg/dl and 1.48±1.16, respectively) (P < 0.02, Table 2). However, there was no significant difference between the mean serum Cu level of these patients (117.04±59.95 μg/dl) and that of patients with type III skin (112.67±59.66 μg/dl) (P > 0.05). The patients with a history of other autoimmune diseases had a higher serum Cu, Zn, and Cu/Zn ratio than patients without a history of autoimmune disease (P < 0.01) (Table 2). We divided the patients into two groups of early-onset (the first onset before the age 50) and late-onset (the first onset after the age 50). Patients with an early-onset of vitiligo had lower serum Cu (107.12±61.17 μg/dl, P = 0.035) and Zn (83.06±49.89 μg/dl, P = 0.001) than those in patients with late onset (122.53±56.30 and 112.81±67.19 μg/dl, respectively) (Table 2). In patients with early-onset vitiligo, the male subjects had significantly higher serum Zn, but a lower Cu/Zn ratio than female subjects (P < 0.01) (Table 2). Among the patients with the late-onset vitiligo, the serum copper concentration and the copper-zinc ratio.

**Table 2.** Selected clinical features of vitiligo patients and serum Cu and Zn levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Cu (μg/dl)</th>
<th>Cu (μg/dl)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Zn (μg/dl)</th>
<th>Zn (μg/dl)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>{[Cu]/[Zn]}</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Onset &lt; 50 (59.83%)</td>
<td>95.07</td>
<td>107.12 ± 61.17</td>
<td>0.035</td>
<td>72.56</td>
<td>83.06 ± 49.89</td>
<td>0.001</td>
<td>1.96 ± 1.44</td>
<td>0.164</td>
</tr>
<tr>
<td>Late Onset &gt;50 (40.17%)</td>
<td>138.37</td>
<td>122.53 ± 56.30</td>
<td></td>
<td>100.23</td>
<td>112.81 ± 67.19</td>
<td>1.72 ± 2.13</td>
<td></td>
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<tr>
<td>Early-Onset (&lt;50 y) Male (23.9%)</td>
<td>98.41</td>
<td>110.78 ± 62.80</td>
<td>0.189</td>
<td>76.92</td>
<td>89.70 ± 45.13</td>
<td>0.008</td>
<td>1.73 ± 1.61</td>
<td>0.00</td>
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<tr>
<td></td>
<td>90.04</td>
<td>116.5 ± 54.15</td>
<td></td>
<td>68.96</td>
<td>78.63 ± 52.90</td>
<td></td>
<td>1.77 ± 2.00</td>
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</tr>
<tr>
<td>Late-Onset (&gt;50 Y) Male (17.1%)</td>
<td>131.69</td>
<td>119.63 ± 57.57</td>
<td>0.017</td>
<td>88.58</td>
<td>113.54 ± 78.26</td>
<td>0.019</td>
<td>1.49 ± 1.11</td>
<td>0.005</td>
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<tr>
<td></td>
<td>128.67</td>
<td>124.52 ± 56.34</td>
<td></td>
<td>100.23</td>
<td>112.27 ± 59.25</td>
<td>0.629</td>
<td>2.54 ± 2.79</td>
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<tr>
<td>Clinical type</td>
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<tr>
<td>Generalized (82.9%)</td>
<td>101.96</td>
<td>111.63 ± 54.18</td>
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<td>73.01</td>
<td>93.11 ± 59.33</td>
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<td>1.88 ± 2.02</td>
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<tr>
<td>Localized (17.09%)</td>
<td>104.72</td>
<td>120.74 ± 71.64</td>
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<td>110.50</td>
<td>98.69 ± 58.63</td>
<td>1.40 ± 1.24</td>
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<tr>
<td>Skin phototype</td>
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<tr>
<td>Skin type I and II (0%)</td>
<td>103.41</td>
<td>112.67 ± 59.66</td>
<td>0.113</td>
<td>84.68</td>
<td>99.24 ± 59.91</td>
<td>0.015</td>
<td>1.48 ± 1.16</td>
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<td>Skin type III (69.93%)</td>
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<tr>
<td>Skin type IV (29.79%)</td>
<td>103.61</td>
<td>117.04 ± 59.95</td>
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<td>67.32</td>
<td>86.16 ± 60.62</td>
<td>2.45 ± 2.75</td>
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<td>History of other</td>
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<td>autoimmune disease</td>
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<tr>
<td>Yes (6.84%)</td>
<td>136.36</td>
<td>143.99 ± 62.61</td>
<td>0.001</td>
<td>74.48</td>
<td>98.29 ± 68.92</td>
<td>0.008</td>
<td>2.08 ± 1.33</td>
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<tr>
<td>No (93.16%)</td>
<td>98.15</td>
<td>111.34 ± 58.89</td>
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<td>77.08</td>
<td>94.71 ± 58.59</td>
<td></td>
<td>1.79 ± 1.96</td>
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<td>Smoking status</td>
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<tr>
<td>Smokers (16.23%)</td>
<td>99.86</td>
<td>106.93 ± 57.08</td>
<td>0.023</td>
<td>74.03</td>
<td>99.67 ± 59.49</td>
<td>0.05</td>
<td>1.71 ± 1.63</td>
<td>0.273</td>
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<td>Non-smokers (83.76%)</td>
<td>103.51</td>
<td>115.45 ± 60.20</td>
<td></td>
<td>76.25</td>
<td>94.34 ± 59.50</td>
<td></td>
<td>1.83 ± 1.95</td>
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</tbody>
</table>

Cu = copper; SD = standard deviation; Y = years; Zn = zinc.
P<sup>a</sup>, case–case comparison.
cofactors for as many as forty metallo-enzymes involved in the skin pigmentation process. These two trace elements are essential cofactors of tyrosinase and superoxide dismutase, two enzymes that are widespread in the human skin and are specifically involved in skin pigmentation and melanocytes protection against free radicals [13,15,27].

There are conflicting reports on the relationship between serum Cu and Zn concentrations and vitiligo. Some authors have reported that compared with healthy controls, the serum Zn, but not Cu levels in vitiligo patients have undergone significant changes [7,28,31]. A recent case-control study of 100 vitiligo patients from India reported decreased serum Zn, but increased Cu levels as compared with healthy individuals [32]. Arora et al found no significant difference between serum Cu and Zn levels in patients with vitiligo and the healthy control group [22]. A meta-analysis of 16 studies conducted to compare the serum Cu and Zn concentrations among 891 vitiligo patients and 1682 healthy controls, demonstrated that the serum Cu and Zn concentrations were significantly lower in the cases than controls (P < 0.0001) [27]. The controversy about the changes of serum Cu and Zn levels in patients with vitiligo prompted us to carry out this study to investigate the relationship between the serum levels of Cu and Zn and the clinical parameters of vitiligo.

Of female patients was higher than those in male patients (P < 0.02). In these cases, the serum levels of Cu were significantly lower (P = 0.023), but Zn levels were higher in smokers than those in non-smoker patients (P = 0.05) (Table 2).

We also evaluated the association between serum Cu and Zn levels and the patients’ clinical data. The serum Cu levels showed a positive correlation with the early age of the disease onset (r = 0.251, P = 0.039). We found a significant positive correlation between serum Cu concentration and duration of disease (Spearman correlation test, r = 0.256, P = 0.01). However, the correlation coefficient only reached statistical significance in females (r = 0.225, P = 0.034), but not in male patients (Table 3). We also observed a positive correlation between serum Cu and Zn levels and segmental Vitiligo (r = 0.20, P = 0.045). There was no correlation between the levels of two serum trace elements and other parameters including skin and clinical types of the disease (Table 3).

<table>
<thead>
<tr>
<th>Correlation between</th>
<th>r (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cu and serum Zn</td>
<td>0.144 (0.252)</td>
</tr>
<tr>
<td>Serum Cu and age of onset Early onset</td>
<td>0.251 (0.039)</td>
</tr>
<tr>
<td>Late onset</td>
<td>0.042 (0.774)</td>
</tr>
<tr>
<td>Serum Zn and age of onset Early onset</td>
<td>0.157 (0.362)</td>
</tr>
<tr>
<td>Late onset</td>
<td>0.189 (0.175)</td>
</tr>
<tr>
<td>Serum Cu or Zn and skin type Type III</td>
<td>0.207 (0.097)</td>
</tr>
<tr>
<td>Type IV</td>
<td>0.071 (0.688)</td>
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<td>Serum Cu or Zn and clinical type of vitiligo Generalized</td>
<td>0.022 (0.844)</td>
</tr>
<tr>
<td>Localized</td>
<td>0.453 (0.105)</td>
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<td>Serum Cu or Zn and clinical type of vitiligo Segmental</td>
<td>0.20 (0.045)</td>
</tr>
<tr>
<td>Non-segmental</td>
<td>0.062 (0.666)</td>
</tr>
<tr>
<td>Serum Zn and the duration of disease Early onset</td>
<td>-0.018 (0.862)</td>
</tr>
<tr>
<td>Late onset</td>
<td>0.256 (0.010)</td>
</tr>
<tr>
<td>Serum Zn in male and the duration of disease</td>
<td>-0.186 (0.252)</td>
</tr>
<tr>
<td>Serum Zn in female and the duration of disease</td>
<td>0.058 (0.662)</td>
</tr>
<tr>
<td>Serum Cu in male and the duration of disease</td>
<td>0.112 (0.448)</td>
</tr>
<tr>
<td>Serum Cu in female and the duration of disease</td>
<td>0.225 (0.034)</td>
</tr>
</tbody>
</table>

Cu = copper; Zn = zinc.

Table 3. Spearman correlation coefficient (r) and P value between serum Cu, Zn, age of onset and gender in patients

Conclusions

Numerous studies have shown a role for the oxidant–antioxidant imbalance and accumulation of ROS in the skin lesion of vitiligo patients [7,10,20]. Cu and Zn are necessary cofactors for as many as forty metallo-enzymes involved in the skin pigmentation process. These two trace elements are essential cofactors of tyrosinase and superoxide dismutase, two enzymes that are widespread in the human skin and are specifically involved in skin pigmentation and melanocytes protection against free radicals, respectively [13,15,27]. There are conflicting reports on the relationship between serum Cu and Zn concentrations and vitiligo. Some authors have reported that compared with healthy controls, the serum Zn, but not Cu levels in vitiligo patients have undergone significant changes [7,28,31]. A recent case-control study of 100 vitiligo patients from India reported decreased serum Zn, but increased Cu levels as compared with healthy individuals [32]. Arora et al found no significant difference between serum Zn levels of vitiligo patients and the healthy control group [22]. A meta-analysis of 16 studies conducted to compare the serum Cu and Zn concentrations among 891 vitiligo patients and 1682 healthy controls, demonstrated that the serum Cu and Zn concentrations were significantly lower in the cases than controls (P < 0.0001) [27]. The controversy about the changes of serum Cu and Zn levels in patients with vitiligo prompted us to carry out this study to investigate the relationship between the serum levels of Cu and Zn and the clinical parameters of vitiligo.
these trace elements and the pathogenesis of vitiligo among a group of Iranian patients.

In our study, the median serum Cu and Zn levels in both the localized (104.72 and 110.50 µg/dl, respectively) and generalized vitiligo patients (101.96 and 73.01 µg/dl, respectively) were significantly less than those in the control group (138.58 and 118.42 µg/dl, respectively). Compared with the control group, the mean serum levels of Cu and Zn in the patients group were also significantly lower in male and female vitiligo patients, as compared to their healthy counterparts (Table 1). Our results are consistent with the findings of Zeng et al. who reported a significant reduction in serum concentrations of both Cu and Zn in Chinese vitiligo patients [27]. Since both the increased and decreased levels of trace elements can affect the activity of antioxidant enzymes and oxidative stress, a U-shaped relation between zinc and copper status and optimal health condition has been proposed [33]. Thus, the conflicting reports regarding the changes in the level of these trace elements in vitiligo might be true findings. Otherwise, the discordance could be linked to the sample size, racial, or environmental factors such as diet variety.

In our study, the mean concentration of serum Cu in smoker patients (106.93 ± 57.08 µg/dl) was lower, but the mean Zn levels (99.67 ± 59.49 µg/dl) was higher than those in non-smoker patients (115.45 ± 60.20 µg/dl and 94.34± 59.50 µg/dl, respectively) (P ≤ 0.05). It has been suggested that there is a close relation between Cu/Zn ratio and systemic oxidative state and the balance between serum Cu and Zn is clinically more important than their concentrations in serum [17,34]. Wacewicz et al found a significantly higher Cu/Zn ratio in the serum of vitiligo patients as compared to healthy controls [35]. A previous study on 151 cases of three groups of skin diseases including skin cancer, inflammatory, and non-inflammatory diseases reported that the serum Cu/Zn ratio among examined patients was higher than the control group and reflected the clinical severity in each disease group [36]. We also found a higher Cu/Zn ratio among vitiligo patients (1.81 ± 1.90) than healthy controls (1.28 ± 0.573), but the difference was not statically significant (P = 0.49, Table 1). We observed a higher serum Cu/Zn ratio in young (1.96 ± 2.09) and male cases (1.67 ± 1.48), as compared to their healthy counterparts (1.24 ± 0.438 and 1.11 ± 0.338, respectively) (P = 0.01).

A linear regression analysis showed positive correlations between serum Cu and the early age of onset (r = 0.251, P = 0.039) and the segmental type of the disease (r = 0.2, P = 0.045) (Table 3). A significant positive correlation was also observed between serum Cu concentrations and the duration of disease, especially in the female patients (r=0.225, P = 0.034). No significant correlation was observed between serum Cu and Zn levels and other parameters in either patients or the control group. Some previous studies detected no correlation between serum Cu and Zn levels and the disease subgroups [37,38]. But, others reported a negative correlation between serum levels of Zn and the generalized vitiligo, age, and duration of disease [28,31].

In a study of tissue copper in vitiligo patients, the mean lesion (1.3 µg/g) and non-lesion (1.4 µg/g) Cu levels were non-significantly lower than tissue Cu levels of the control group (1.9 µg/g) [39]. Melanin has a high affinity for the sequestration of metal ions, and pigmented tissues contain a significant amount of metal cations including Cu and Zn [12]. By binding and sequestering metal ions, melanosomes are protected from oxidative damage. The serum concentrations of Zn and Cu have been reported to increase with age [30,40,41]. In our study, the elderly patients (≥ 50 years) had significantly higher serum Cu and Zn concentrations than young (< 50 years) patients (P = 0.00) (Table 1). In the case-control comparison, both the elderly and young patients had lower serum Cu levels than their respective healthy controls (P ≤ 0.05). The young patients also had significantly lower serum Zn levels than the respective control group, but no significant difference was found in terms of serum Zn concentration between elderly patients and their respective elderly control group (P > 0.05). A relationship between vitiligo and the incidence of other autoimmune disorders has been suggested [42,43]. In our study, 6.8% of vitiligo patients had a history of other autoimmune diseases including rheumatoid arthritis, type 1 diabetes mellitus, and hypothyroidism. Several previous studies have suggested an association between Zn and Cu deficiency and hypopigmentation of the skin and hair, immune defects, and autoimmune diseases like type 1 diabetes, rheumatoid arthritis, multiple sclerosis, systemic Lupus erythematosus, celiac disease, Hashimoto thyroiditis, and juvenile idiopathic arthritis [44,45].

In the current study, the median and mean serum Cu and Zn concentrations in the generalized form of vitiligo were less than those in the localized form (P ≤ 0.05). Mirnezami et al also reported significantly lower zinc levels in the generalized vitiligo than the localized form [28].

In conclusion, our results are consistent with prior study findings of decreased and imbalanced levels of serum Cu and Zn in vitiligo patients. The main drawback of this study was the relatively small sample size that limited the statistical power to perform analyses across all subgroups of patients. Future studies with a larger sample size should be conducted to understand the etiopathogenic roles and the potential therapeutic benefits of Cu and Zn supplementation for vitiligo patients.
Acknowledgements

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Dermoscopic Differentiation of Blister Beetle Dermatitis and Herpes Zoster: an Observational Study

Balachandra Suryakant Ankad1, Varsha R. Koti1, Aimilios Lallas2

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Key words: dermoscopy, blister beetle dermatitis, herpes zoster, bullous disorders


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ABSTRACT

Introduction: Blister beetle dermatitis (BBD) and herpes zoster (HZ) manifest suddenly with vesicular lesions mimicking each other and progress rapidly. But a lack of definite differentiating criteria yearns the need for better investigating modality. Though histopathology persuades the need, is an invasive procedure, commonly deferred. Thus, dermoscopy, a non-invasive rapid diagnostic tool, can help in differentiating.

Objectives: To evaluate different dermoscopic patterns of BBD and HZ to differentiate both and to study dermoscopic features in early and late stages of lesions.

Methods: An observational cross-section study conducted in southern India. Nine patients with clinical features suggestive of BBD and HZ were recruited. Lesions were divided arbitrarily into early and late. Dermoscopic examination was performed with handheld dermoscope. Diagnosis was confirmed by skin biopsy and Tzanck smear wherever necessary. Statistical analysis performed using data in terms of frequencies and percentages.

Results: Dermoscopy of early BBD lesions showed multiple discrete and confluent yellowish-white structures, brown dots, roundish white globules, gray structures, ‘targetoid pattern’, brown areas over intense reddish pink background. Late BBD lesions revealed pinkish-white area, reduced gray structures and, dotted and globular vessels. Early HZ lesions showed poly-lobular gray and brown globules, bright pink background, gray globules covered by grayish veil-like structure with gray rim. Late HZ lesions revealed ‘solar eclipse’ pattern and ‘crumpled fabric’ patterns. The dermoscopic findings correlated with histopathology.

Conclusions: Dermoscopic patterns show peculiar features consistently pertaining to BBD and HZ, thus help in early diagnosis assisting in accurate treatment in both conditions.
Introduction

Paederus dermatitis, well known as dermatitis linearis or blister beetle dermatitis (BBD) is an irritant contact dermatitis following exposure of an insect belonging to the genus Paederus [1]. Accidental crushing of the beetle over the skin releases hemolymph containing a potent vesicant, paederine [2]. It is characterized with sudden onset of erythematous, edematous lesions in linear whiplash appearance over exposed areas or kissing lesions in opposing areas.

Herpes zoster (HZ) is a segmental eruption due to reactivation of latent varicella zoster virus from dorsal root ganglion which presents as closely grouped papules, rapidly becoming vesicular and pustular; develop in one or more contiguous dermatomes with sharp cut off at the midline [3]. BBD and HZ manifest suddenly with vesicular lesions and progress rapidly in the disease process. Lesions of both entity are associated with pain and burning sensation and hence they mimic each other morphologically and symptomatically [4,5]. Thus, both lesions should be diagnosed with accuracy. There are no defined criteria to differentiate both conditions clinically. However, histopathology plays an important role to distinguish. Many times, patients may not agree for the same.

Dermoscopy is a rapid, non-invasive tool which helps to visualize surface and sub surface features that are not visible to naked eyes [6]. Dermoscopy of BBD is explained in a single case report till date [7] and limited descriptions on dermoscopic patterns in HZ are present in the literature [8,9,10]. Furthermore, there is a hiatus in the dermoscopic distinction between the two. In this study, we evaluated the dermoscopic features of BBD and HZ.

Objectives

To evaluate different dermoscopic patterns in distinction of BBD and HZ.

Methods

This study was conducted in southern India between January 2021 and May 2021. The approval from the institutional review board was taken and an informed written consent was obtained from patients. It was an observational cross-section analysis. The patients with clinical features suggestive of BBD and HZ were analyzed for demographic details in terms of age, sex and occupation. Vesicular lesions with classical features without history of previous treatment were included in the inclusion criteria. Exclusion criteria included lesions with super-added infection. Lesions were divided arbitrarily into early and late. Lesions with less and more than 3 days were considered as early and late lesions respectively. Physical examination and hematological investigations were done to assess the systemic involvement.

Dermoscopic examination of target lesion was done with handheld dermoscope with 10x magnification using ultrasound gel as interface medium. Care was taken avoid pressure on the lesions. Dermoscopic analysis was done by one of the authors (BSA). Diagnosis was confirmed by skin biopsy and Tzanck smear wherever necessary.

Results

This study included 9 patients with 6 (66.6%) males and 3 (33.3%) females. Age of patients ranged from 10 years to 70 years (mean age 35 years). Five (55.5%) patients had BBD with erythematous and linear lesions with crusting and vesicles with burning sensation over exposed body parts (Figures 1A, 2A, 3A, and 4A). One patient was followed up (5 days) for the healed lesion (Figure 5A). Biopsy was performed in two patients clinically diagnosed with BBD and in

![Figure 1. (A) Clinical image of early lesion of blister beetle dermatitis involving malar eminence and left eyelids unilaterally. (B) Dermoscopy reveals presence of multiple discrete and confluent yellowish-white structures (star) and brown globules (arrow) indicating excoriation with white scales.](image-url)
Figure 2. (A) Clinical image of early lesion of blister beetle dermatitis over nape of neck. (B) Dermoscopy shows gray structure (yellow star), multiple brown dots/globules (red arrows), and brown areas (green star) with roundish white globules (red star) over the pink background. Few white globules show brown dots (blue circle) in the center in a targetoid pattern.

Figure 3. (A) Clinical image of early lesion of blister beetle dermatitis over right shoulder. (B) Dermoscopy shows brownish structureless area (green star) in center surrounded by confluent gray structures (yellow star) with gray (yellow circles) and brown dots (red arrow) on pink background. Note the white scales (black arrow) surrounding the brown dots and globules.

Figure 4. (A) Clinical image of late lesion of blister beetle dermatitis over peri-orbital region. (B) Dermoscopy reveals multiple confluent gray structures (yellow star), brown areas (green star) and white globules (red star) with brown globules (red arrow). Pinkish-white structureless area (black star) and gray globules (yellow circle) are well appreciated on a pinkish background.
HZ lesions were distributed in the ophthalmic branch of trigeminal nerve (Figures 6A and 7A) and thoracic, cervical nerves (Figures 8A and 9A), as closely grouped red papules and vesicles on erythematous background. Four (44.4%) patients with HZ were included in the study.

**Dermoscopy of Early HZ Lesions**
Polylobular gray and brown globules over a bright pink background were noted with gray globules covered by grayish veil-like structure with gray rim. Yellowish-orange structure surrounding the pigment globules, red areas and scales were seen (Figures 6B, 7B and 8B).

**Dermoscopy of Late HZ Lesions**
Similar pattern were observed but for the reduced gray structures in addition to pinkish-white areas (Figure 9B). Few lesions revealed dotted and globular vessels, scales on a pinkish-white background (Figure 5B).

One patient with HZ. Tzanck smear was performed in two patients clinically suspecting with HZ to see for acantholytic cells and multinucleated giant cells.

**Dermoscopy of Early BBD Lesions**
Multiple discrete and confluent yellowish-white structures, brown dots (Figure 1B) with roundish white globules, gray structures and brown areas (Figures 2B and 3B) over intense reddish pink background. Few roundish white globules showed brownish pigmentation at its center (Figure 2B). White scales around the brown globules were other features (Figure 3B).

**Dermoscopy of Late BBD Lesions**
Similar pattern were observed but for the reduced gray structures in addition to pinkish-white areas (Figure 4B). Few lesions revealed dotted and globular vessels, scales on a pinkish-white background (Figure 5B).

HZ lesions were distributed in the ophthalmic branch of trigeminal nerve (Figures 6A and 7A) and thoracic, cervical nerves (Figures 8A and 9A), as closely grouped red papules and vesicles on erythematous background. Four (44.4%) patients with HZ were included in the study.

**Dermoscopy of Early HZ Lesions**
Polylobular gray and brown globules over a bright pink background were noted with gray globules were covered by grayish veil-like structure with gray rim. Yellowish-orange structure surrounding the pigment globules, red areas and scales were seen (Figures 6B, 7B and 8B).

**Dermoscopy of Late HZ Lesions**
Polylobular gray and brown structures surrounded by erythematous zone resembling a ‘solar eclipse’ pattern were observed with multiple brown and gray dots (Figures 9B and 9C). ‘Crumpled fabric’ appearance which describes
folding of roof of flaccid bullae in late lesions was noted (Figures 9B and 9C) [8]. There was increased intensity of gray structures observed in late HZ lesions when compared to late lesions of BBD. Dermoscopic differentiation between BBD and HZ is depicted in Table 1.

Conclusions

Dermoscopy being a rapid, non-invasive diagnostic tool, that demonstrates features which correlate well with histopathological changes. Furthermore it also reveals the changes that take place in the different layers of skin by which one can study the disease evolution process. This study is aimed at differentiating BBD from HZ in a dermoscopic perspective. Clinically BBD manifests as fluid filled and necrotic lesions with pain and burning sensation [11]. The differentials include herpes simplex, HZ or contact irritant dermatitis [12].

Dermoscopic analysis of BBD is very sparse in the literature and limited to a single case report. Authors noted...
Yellowish-white globules indicate spongiotic vesicles with serum within the epidermis and white roundish globules are suggestive of micro-pustules (Figure 10). Gray structure is due to necrotic pigmented epithelium with non-pigmented regenerating epithelium. In contrast, brown dots are due to necrotic keratinocytes with retained melanin. Brown areas represent dried serum and necrotic keratinocytes with retained melanin. Scales and pink background correspond to hyperkeratosis and vasodilatation respectively. White globules with brown dots in the centre are suggestive of perifollicular micropustule.

HZ shows ballooning degeneration of necrotic keratinocytes within intra-epidermal blister and few multinucleated giant cells at the base of blister in histopathology. Dermal small vessel vasculitis is a characteristic feature [14].

<table>
<thead>
<tr>
<th>Dermoscopic features</th>
<th>Blister beetle dermatitis</th>
<th>Herpes zoster</th>
</tr>
</thead>
</table>
| Early lesions        | • Discrete and confluent yellowish-white structures.  
                          • Brown dots with roundish white globules, gray structures and brown areas.  
                          • White scales.  
                          • Background: intense reddish pink. | • Poly-lobular gray and brown globules.  
                          • Gray globules covered by grayish veil-like structure with gray rim.  
                          • Yellowish-orange structure surrounding the pigment globules and red areas.  
                          • Scales present.  
                          • Background: bright pink. |
| Late lesions         | • Decreased amount of gray structures.  
                          • Vessel morphology: dotted and globular vessel.  
                          • Scales present.  
                          • Background: pinkish-white | • Increased intensity of gray structures.  
                          • ‘Solar eclipse’ pattern  
                          • Multiple brown and gray dots.  
                          • ‘Crumpled fabric’ appearance. |

Figure 9. (A) Clinical image of late lesion of herpes zoster involving right shoulder and arm. (B and C) Dermoscopy shows poly-lobular gray (yellow stars) and brown (red arrows) structures surrounded by erythematous zone (black stars). Note the brown and gray dots (yellow arrows) and the ‘crumpled fabric’ appearance (white circle) and ‘solar eclipse’ pattern (yellow box).

Table 1. Dermoscopic differences between blister beetle dermatitis and herpes zoster.
Dilated vessels (Figure 11). The brown dots and globules are due to dried serum, necrotic keratinocytes and melanin retention. Scaling is due to hyperkeratosis [8,9]. The white linear folds / 'crumpled fabric' appearance were due to folding of superficial keratinocytes (roof) due to flaccidity was observed in late lesions of HZ. This was previously reported only in pemphigus vulgaris, pemphigus foliaceous and Hailey-Hailey disease (as 'crumpled fabric appearance') [8]. This appearance is expected in older bullous lesions with flaccidity of bullae.

Multiple poly-lobular gray globules correlated to the necrotic keratinocytes within the intra-epidermal vesicle. The grayish veil-like structure is due to the non-pigmented epithelium of the basal keratinocytes with overlying necrotic pigmented keratinocytes within the vesicular fluid. Gray rim is because of edge of vesicle that is seen vertically under dermoscopy. Yellowish-orange structure corresponds to serum and extra-vasated erythrocytes within the intra-epidermal vesicle. Erythematous background correlates with the increased vascularity and red dots with dilated vessels (Figure 11). The brown dots and globules are due to dried serum, necrotic keratinocytes and melanin retention. Scaling is due to hyperkeratosis [8,9]. The white linear folds / 'crumpled fabric' appearance were due to folding of superficial keratinocytes (roof) due to flaccidity was observed in late lesions of HZ. This was previously reported only in pemphigus vulgaris, pemphigus foliaceous and Hailey-Hailey disease (as 'crumpled fabric appearance') [8]. This appearance is expected in older bullous lesions with flaccidity of bullae.
Thus, the dermoscopic features are fairly distinguishable in BBD and HZ (Table 1). They correlate well with corresponding histopathological changes (Table 2). The dermoscopic patterns observed in our study correlated well with the study by Narkhede et al [8], in evaluation of HZ, but the characterization of lesions into early and late lesions pertaining to duration of onset was not depicted. This is required as any intervention with antiviral therapy within 72 hours of onset of rash, reduces the risk of ophthalmic complications, has effect on severity of acute pain, faster healing of lesions and shortens the duration of post herpetic neuralgia [15,16].

As the lesions of BBD and HZ closely simulate each other, the dermoscopic differentiation thus helps in early diagnosis and management, as the line of management differs in the two and minimizes the morbidity and the social stigma associated with HZ. Limitations of this study include small sample size, histopathology was not done in all the lesions, and study was conducted in a single center.

Thus, the use of dermoscopy has spread its wings from infectious to inflammatory and to malignant conditions, and from being a diagnostic tool to a therapeutic monitoring tool. Here, we observed significant dermoscopic differences between BBD and HZ even at their earliest presentation, thus helping the dermatologists in further management of the conditions. It is thus a dermatologist's stethoscope.

### Table 2. Dermoscopic histopathological correlation of blister beetle dermatitis and herpes zoster.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Dermoscopic features</th>
<th>Histopathological correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blister beetle dermatitis</strong></td>
<td>Discrete and confluent yellowish-white structures.</td>
<td>Spongiotic vesicles with necrosis of the epidermis</td>
</tr>
<tr>
<td></td>
<td>White globules</td>
<td>Micro-pustules in epidermis</td>
</tr>
<tr>
<td></td>
<td>Gray structures</td>
<td>Necrotic pigmented epithelium with regenerating non-pigmented epithelium</td>
</tr>
<tr>
<td></td>
<td>Brown areas</td>
<td>Dried serum and necrotic keratinocytes with retained melanin</td>
</tr>
<tr>
<td></td>
<td>White scales</td>
<td>Hyperkeratosis</td>
</tr>
<tr>
<td></td>
<td>Dotted and globular vessels.</td>
<td>Superficial peri-vascular infiltration with vasodilation of dermal vessels.</td>
</tr>
<tr>
<td></td>
<td>Intense reddish pink background.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>White globules with brown dots in the centre</td>
<td>Perifollicular micro-pustule.</td>
</tr>
<tr>
<td><strong>Herpes zoster</strong></td>
<td>Multiple poly-lobular gray globules</td>
<td>Necrotic keratinocytes within intra-epidermal vesicle</td>
</tr>
<tr>
<td></td>
<td>Greyish veil-like structure</td>
<td>Pigmented epithelium overlying the vesicle.</td>
</tr>
<tr>
<td></td>
<td>Grey rim</td>
<td>Edge of the vesicle</td>
</tr>
<tr>
<td></td>
<td>Yellowish orange structure</td>
<td>Serum and extra-vasated erythrocytes within the intra-epidermal vesicle</td>
</tr>
<tr>
<td></td>
<td>Erythematous background</td>
<td>Increased vascularity</td>
</tr>
<tr>
<td></td>
<td>Red dots</td>
<td>Dilated vessels and vasculitis</td>
</tr>
<tr>
<td></td>
<td>Brown dots and globules</td>
<td>Dried serum, necrotic keratinocytes and melanin retention</td>
</tr>
<tr>
<td></td>
<td>Crumpled fabric appearance</td>
<td>Roof of flaccid blister</td>
</tr>
<tr>
<td></td>
<td>Scales</td>
<td>Hyperkeratosis</td>
</tr>
</tbody>
</table>

#### References

Indications for Digital Monitoring of Patients With Multiple Nevi: Recommendations from the International Dermoscopy Society

Teresa Russo¹, Vincenzo Piccolo¹, Elvira Moscarella¹, Philipp Tschandl², Harald Kittler², John Paoli³, Aimilios Lallas⁴, Ralph P. Braun⁵, Luc Thomas⁶, H. Peter Soyer⁷, Josep Malvehy⁸, Susana Puig⁸, Ashfaq Marghoob⁹, Alon Scope¹⁰, Andreas Blum¹¹, Allan C. Halpern¹², Horacio Cabo¹², Scott Menzies¹³, Wilhelm Stolz¹⁴, Masaru Tanaka¹⁵, Harold Rabinovitz¹⁶, Rainer Hofmann-Wellenhof¹⁷, Renato Marchiori Bakos¹⁸, Iris Zalaudek¹⁹, Giovanni Pellacani²⁰, Ana Varela Veiga²¹, Laura Rosende Maceiras²¹, Cristina de las Heras-Sotos²¹, Giuseppe Argenziano¹

Key words: dermoscopy, dermatoscopy, digital monitoring, multiple nevi, total body photography


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Introduction

A combined clinical and dermoscopic examination of melanocytic lesions allows for the recognition of most melanomas at a baseline visit [1-3]. In a patient with a single doubtful lesion, although only moderately atypical, the best approach is prompt excision and histopathologic examination. Conversely, in patients with multiple nevi, the approach of excising any atypical lesion appears neither reasonable nor cost-effective. In this scenario, sequential monitoring and imaging using total body skin photography (TBSP) coupled with digital dermoscopy (DD) documentation represents the best approach to minimize unnecessary excisions while maximizing early detection of melanoma (Figures 1 and 2). While DD is useful to evaluate morphologic changes of the individual monitored lesions, TBSP mostly helps in the recognition of new lesions or significant changes in lesions that were not previously documented dermoscopically [2-7].

It has been calculated that about 10% of melanomas are diagnosed over time in the context of clinically and dermoscopically inconspicuous tumors in patients with multiple and/or atypical nevi [1,2]. In a recent cohort study dealing with high-risk patients in a melanoma dermatology clinic, 60.8% of melanomas were found with the assistance of TBSP (31.6%) or sequential DD imaging (29.2%) [3]. Melanomas detected via sequential monitoring with TBSP and DD usually escape baseline detection because they neither display melanoma-specific criteria, nor substantially differ from the patients’ nevi [9]. This more frequently occurs in individuals with peculiar nevus phenotypes, such as familial melanoma patients [10]. However, TBSP and DD are time-consuming techniques, so appropriate indications are crucial for the method to be effective. Recently, a study by Haenssle et al on 688 patients concluded that patients with multiple nevi and additional risk factors for melanoma had the highest benefit from sequential DD imaging in terms of early melanoma detection over time [6,7]. Several additional studies deal with the relevant additional risk factors to be evaluated when referring a patient for digital monitoring, but there is some heterogeneity among them [11-14]. Since a consensus agreement is still lacking, we are trying to provide one.

Objectives

The purpose of this study was, therefore, to set up a list of indications for digital follow-up performed via TBSP coupled with DD through the selection of specific melanoma risk factors that may serve to better recognize patients who will benefit from this approach.
Methods

This study was performed on behalf of the International Dermoscopy Society (IDS), with consensus obtained through the e-Delphi methodology [15]. Participants were recruited among the executive board members of the IDS who were specifically asked by email invitation for their consent to take part in the study. Only those who accepted to join the project received the SurveyMonkey (https://www.surveymonkey.com/) link and password for taking part in the survey.

The study consisted of two steps: (I) identification of major risk factors for melanoma in patients with multiple nevi according to the most relevant meta-analyses and studies; and (II) selection of indications for TBSP and DD after a three-round questionnaire proposed to a panel of international experts in dermoscopy. During each round, participants were
given a 4-week period to complete the survey and reminders were sent to non-responders on days 7, 14 and 21. The three rounds were conducted over a 6-month period and the final list of indications was obtained and completed within 8 months. The aforementioned criteria for the enrolment of patients for digital monitoring programs were finally drawn up with the collaboration of expert members of the IDS, who contributed to the study with their answers, advice and feedback.

**Step 1: Identification of Risk Factors for Melanoma in Patients With Multiple Nevi**

The questions for the survey were obtained after a literature search of relevant meta-analyses and studies about major melanoma risk factors. The presence of multiple nevi was considered the basic requirement for patient enrolment in a digital monitoring program using TBSP coupled with DD. The number and type of nevi needed to reach the cut-off point were discussed in the second step. The lower size limit to consider the nevus eligible to be counted has been conventionally established at 2 mm. The proposed questions were associated with their background studies and their relative levels of evidence assigned based on the Oxford 2011 Levels of Evidence [16]. Melanoma risk factors were expressed in terms of relative risk (RR) and odds ratio (OR) with the exception of CDKN2A mutation [17-21], for which we considered the ratio between lifetime risk of melanoma in patients with the mutation and lifetime risk in the general population (Table 1). Variables increasing the melanoma risk at least 3 times were considered as major risk factors; variables increasing the risk between 2 and 3 times were considered as intermediate risk factors; and variables increasing the risk by less than 2 times were considered as minor risk factors [22].

### Step 2: Selection of Indications for TBSP and DD After a Three-round Questionnaire Proposed to a Panel of International Experts in Dermoscopy

Participants were first asked if a given risk factor, in combination with the presence of multiple nevi, is relevant enough to justify inclusion in the list of indications. The questions were uploaded in two different blinded Delphi rounds on the SurveyMonkey platform and were proposed to the experts who were included for the 1st round survey. They were asked to judge their agreement for each sentence using the 5-point given a 4-week period to complete the survey and reminders were sent to non-responders on days 7, 14 and 21. The three rounds were conducted over a 6-month period and the final list of indications was obtained and completed within 8 months. The aforementioned criteria for the enrolment of patients for digital monitoring programs were finally drawn up with the collaboration of expert members of the IDS, who contributed to the study with their answers, advice and feedback.

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### Table 1. Risk factors for cutaneous melanomas and their relative risks (modified from Chen et al [4]).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Risk factor for cutaneous melanoma</th>
<th>Summary statistics (RR, OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common nevi (total number)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-40</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td>41-60</td>
<td>2.24</td>
<td></td>
</tr>
<tr>
<td>61-80</td>
<td>3.26</td>
<td></td>
</tr>
<tr>
<td>81-100</td>
<td>4.74</td>
<td></td>
</tr>
<tr>
<td>101-120</td>
<td>6.89</td>
<td></td>
</tr>
<tr>
<td>Atypical nevi (total number)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.03</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.39</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6.36</td>
<td></td>
</tr>
<tr>
<td>Eye color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>blue</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td>green</td>
<td>1.61</td>
<td></td>
</tr>
<tr>
<td>hazel</td>
<td>1.52</td>
<td></td>
</tr>
<tr>
<td>Hair color</td>
<td></td>
<td></td>
</tr>
<tr>
<td>red</td>
<td>3.64</td>
<td></td>
</tr>
<tr>
<td>blond</td>
<td>1.96</td>
<td></td>
</tr>
<tr>
<td>light brown</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>Family history of melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>Personal history of non-melanoma skin cancer</td>
<td>positive</td>
<td>2.74</td>
</tr>
<tr>
<td>Genetic factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A mutation</td>
<td>10^a</td>
<td></td>
</tr>
<tr>
<td>Sun exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>strong history of sunburn</td>
<td>2.03</td>
<td></td>
</tr>
<tr>
<td>ever use of tanning booth</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>Organ transplant history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>2.38</td>
<td></td>
</tr>
</tbody>
</table>

RR = relative risk; OR = odds ratio.

* For CDKN2A, the risk is based on the ratio between the lifetime risk of melanoma in patients with the mutation and the lifetime risk of melanoma in the general population.
Results

First Round

Of the executive board members of the IDS invited by email, all (N = 27) confirmed their participation and received the link to answer the round 1 questionnaire anonymously. Of them, 25 completed the questionnaire. More than 90% of experts agreed (32%, N = 8) or strongly agreed (64%, N = 16) on the necessity to establish selection criteria for patients with multiple nevi who need digital monitoring. For 92% (N = 23) of participants, the total number of nevi was considered relevant to select these patients.

Table 1 shows the most common risk factors for melanoma and their relative risks. The great majority agreed (88%, N = 22) that significant risk factors for melanoma were those having a RR (relative risk) > 2. Moreover, 92% (N = 23) of participants agreed that patients with multiple nevi and at least one additional risk factor for melanoma could have a higher cumulative risk for melanoma than patients with only one risk factor, thus making them more eligible for long-term digital monitoring.

Participants were asked to propose other factors that should be considered as indication for digital monitoring. Two of 25 participants proposed the anxiety of patients with multiple nevi as a criterion for digital monitoring. Therefore, this criterion was added for the second round of questions. In the open answers, some participants underlined the necessity to avoid digital monitoring in the following clinical scenarios: (i) in children before puberty, even if multiple nevi were present; (ii) in patients with complex health conditions that can render the examination difficult; (iii) in the context of nodular lesions, especially if rapidly changing.

Second Round

The 2nd round questionnaire was sent to the 25 members who completed the first one, with 23 completing the round. At first, this round had the purpose to establish the number and type of nevi needed as cut-off for the definition of a patient with multiple nevi; secondly, the additional criteria for selecting patients suitable for digital monitoring were established.

Fifteen (65%) experts agreed on the definition of a common nevus being a macular or papular symmetrical lesion, smaller than 6 mm in diameter, uniform in color, with well-defined borders and regular overall architecture in dermoscopy. Consequently, an atypical nevus was defined as a flat or slightly raised lesion usually larger than 6 mm, with ill-defined borders, irregular pigmentation, and a mixed pattern dermoscopically.

Given the RR of 3.26 of developing melanoma in patients with 61-80 common nevi [24], 70% (N = 16) of responders agreed to establish the threshold of at least 60 common nevi to select patients requiring digital monitoring, in the absence of additional risk factors. The experts showed their consensus to reduce the threshold to 40 common nevi (RR 2.24) if the patient had additional melanoma risk factors because of a higher cumulative risk of melanoma. However, the experts did not agree on establishing a cut-off number of atypical nevi as an indication for TBSP and DD if this was the only melanoma risk factor of the patient.

For the other melanoma risk factors, we asked whether the anxiety (as suggested by 2 experts) could be an indication for TBSP and DD. Only 52% (N = 12) of participants considered it a relevant risk factor in patients with multiple nevi. This criterion was therefore excluded from the final list of indications.

Nineteen (83%) experts agreed on considering a personal history of melanoma coupled with more than 40 nevi as an indication for TBSP and DD. They also agreed to enlist patients for digital monitoring if they had more than 40 nevi and red hair, with (65%, N = 15) or without a MC1R mutation (74%, N = 17). Organ transplant recipients with at least 40 nevi were also judged suitable for digital monitoring (65%, N = 15). Finally, almost all members agreed (91.3%, N = 21) on considering digital monitoring to be useful in patients with a CDKN2A mutation (familial melanoma) even in patients with less than 40 nevi.

In the open final discussion of this round, with almost total agreement among the experts, it emerged that even if in absence of referring relative risk data, other rarer identified melanoma-predisposing mutations different from CDKN2A and MC1R variants (ie BAP-1, CDK-4, and MIT-F) should not be ignored independently from the nevus count.

There was no agreement on indicating digital monitoring in patients with few atypical nevi or with less than 40 nevi. Personal history of non-melanocytic skin cancer, sunbed exposure or sunburns were not considered as valid criteria to select a patient for TBSP and DD even when associated with the presence of more than 40 nevi.

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Third Round

The results of the second round allowed us to propose the following five indications for digital monitoring in the third round:

1. Patients with more than 60 melanocytic nevi.
2. Patients with a CDKN2A mutation or other rarer high-risk melanoma genetic variants.
3. Patients with more than 40 melanocytic nevi and a personal history of melanoma.
4. Patients with more than 40 melanocytic nevi and red hair and/or a MC1R mutation
5. Patients with more than 40 melanocytic nevi and a history of organ transplantation.

This final list (Table 2) was proposed by mail to the 25 members of the first Delphi round, clarifying that the strategy of silent consensus would be used (i.e. no answer would be interpreted as a positive response). Ultimately, 17 members (68%) confirmed their consensus to this list of criteria, while the remaining participants expressed their silent consensus.

Conclusions

In the last decade, many studies focused on digital monitoring of patients with multiple nevi, with special emphasis on the duration and scheduling of follow-up visits, the type and number of lesions to be digitally documented, and the type of changes that should lead to a biopsy [3-5]. However, no sufficient and exhaustive data have been reported about the indications for patient enrolment to digital monitoring. Being aware of the costs and duration of the TBSP and DD procedure, our aim was to more precisely identify the patient categories that can benefit from this diagnostic approach [24].

A high total number of nevi is clearly the basic condition to include a patient in a digital monitoring program. The participants considered a total nevus count of at least 60 (RR >3) sufficient to refer the patient for digital monitoring. This was based on a meta-analysis published by Gandini et al in 2005 that confirmed such patients’ propensity to develop melanoma [25,26]. In detail, the higher the number of common nevi, the higher the RR for melanoma, which was estimated to be 2.24 for a number of common nevi ranging from 41-60 nevi and 3.26 for 61-80 nevi. Thus, patients with more than 40 nevi (with a RR between 2 and 3) were considered to deserve this follow-up procedure only if presenting with additional risk factors, namely: a personal history of melanoma, red hair with or without a MC1R variant associated to melanoma risk or a history of organ transplantation [25,26].

In the same meta-analysis by Gandini et al, patients with two atypical nevi showed a RR of 2.10 [25,26]. Therefore, we asked participants if patients with multiple nevi (more than 40) and at least 2 atypical nevi should be enrolled for digital monitoring. This criterion probably did not reach a consensus because it is very frequent that a patient with more than 60 nevi also exhibits some atypical ones.

In 2015, Chen et al found a stable 2- to 3-fold increased risk depending on the number of previous melanomas, in both patients with familial melanoma and those with sporadic melanoma(s) [27]. For instance, in patients with a single previous melanoma, the risk for a second melanoma was 2.5 for patients with familial melanoma and 2.3 in patients with a sporadic melanoma. In 2019, Lallas et al in a prospective study in a cohort of 977 patients showed 8% cumulative risk of second primary melanoma, thus highlighting the value of TBSP and DD in this group of patients [28]. According to these findings, the personal history of melanoma (both in familial melanoma and in sporadic melanoma) was judged as a very effective criterion to better select patients for digital monitoring, as also suggested by Haenssle et al [6,7].

In 2010, Wheless et al reported a RR of 2.74 for developing melanoma in patients with a history of NMSC, compared to controls with no prior NMSC [29]. This group of patients, even when having multiple nevi, was not considered eligible for digital monitoring. Given the high prevalence of NMSC, this criterion could potentially increase the number of patients referred for this special follow-up procedure too much, without a real benefit in finding more melanomas over time.

In contrast, almost all participants agreed on including the red hair phenotype in the final list of indications. In a meta-analysis on phenotypic risk factors for cutaneous melanoma, the red hair phenotype was the only phenotypic aspect found to have a RR greater than 3 (3.64) for melanoma development, while all the other clinical features showed a

<table>
<thead>
<tr>
<th>Indications for digital monitoring in patients with multiple nevi.</th>
</tr>
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<tbody>
<tr>
<td>I. Patients with more than 60 melanocytic nevi.</td>
</tr>
<tr>
<td>II. Patients with a CDKN2A mutation or other rarer high-risk melanoma genetic variants.</td>
</tr>
<tr>
<td>III. Patients with more than 40 melanocytic nevi and a personal history of melanoma.</td>
</tr>
<tr>
<td>IV. Patients with more than 40 melanocytic nevi and red hair and/or a MC1R mutation</td>
</tr>
<tr>
<td>V. Patients with more than 40 melanocytic nevi and a history of organ transplantation.</td>
</tr>
</tbody>
</table>

Table 2. List of indications for digital monitoring in patient with multiple nevi.
RR below 2 [5,25,26]. Particularly, different studies, as that of Duffy et al confirmed the importance of the association of a MC1R genotype and the presence of multiple nevi in contributing synergically to increase the individual’s melanoma risk [30-32].

A RR for melanoma of 2.03 was found in a meta-analysis by Gandini et al in case of strong sunburn history [33]. Similarly, a large case-control study from the Nurses Health Study published in 2006 found an OR of 2.06 for “ever” versus “never” usage of tanning booths [34]. Despite this risk, the IDS members did not consider patients with a strong history of sunburn or ever use of tanning booths to be qualified for digital monitoring if they had less than 60 nevi.

Concerning the potentially increased risk of melanoma after organ transplantation, the standardized incidence ratio for melanoma was reported to be 2.38 in this population, indicating a substantially increased risk [5,35,36]. Although other immune deficiencies increase the melanoma risk, their RR is not well calculated yet. Thus, participants reached the consensus to refer patients with a history of organ transplantation to digital monitoring if they have more than 40 nevi.

The only exception to the rule of multiple nevi was made for patients with a known CDKN2A variant. CDKN2A variant carriers have at least a 10-fold risk of melanoma compared to people not carrying the mutation. Moreover, patients with CDKN2A often have more than 50 melanocytic nevi [17-21]. Due to this high risk, participants considered this category of patients deserving digital monitoring independently from the total nevus count.

In the final open discussion, with almost total agreement among the experts, an indication emerged to also consider patients with other rarer melanoma-predisposing mutations different from CDKN2A and MC1R variants (ie CDK-4, BAP-1, MITF, POT1, ACD, TERF2IP and TERT), even if for them the exact relative risk still remains unknown. These rarer patients have multiple nevi and an increased risk of melanoma, therefore they were considered an exception independent from the nevus count [37-40].

In conclusion, this study suggests a list of indications for digital monitoring of patients at high risk for melanoma. This list could be a guide to help in selecting patients who could benefit the most from this time-consuming procedure. However, these criteria should always be integrated with the physicians experience in order to include also those exceptions that may escape using them strictly. Further studies and real-life data are needed to confirm the usefulness of this list of indications in clinical practice.

References


Diagnostic Role of Direct Immunofluorescence Assay in Determining The Etiology of Erythroderma: Experience in a Tertiary Referral Hospital

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Key words: erythroderma, fluorescent antibody technique, immunobullous diseases, pathology

Introduction: Erythroderma is a life-threatening dermatologic emergency which is characterized by diffuse erythema and exfoliation affecting more than 90% of the body surface area. Most common cutaneous diseases associated with erythroderma are systemic contact dermatitis, psoriasis, drug eruption and atopic dermatitis. Clinical-pathological correlation is used to determine the underlying disease. In addition, direct immunofluorescence (DIF) may provide significant clues for etiology of erythroderma especially in the case of autoimmune bullous skin diseases (ABSDs).

Objectives: In our study, we aimed to analyze the demographic data, clinical pre-diagnoses, final diagnosis, histopathological and DIF examination findings, accompanying systemic signs and laboratory abnormalities of erythrodermic patients.

Methods: We conducted a retrospective study of 31 erythroderma patients in a referral hospital between 2014 and 2021. Cutaneous biopsies were taken from all patients for H&E and DIF examination.

Results: Average age was 54.6 ± 23 years, 48.4% of the patients were female (N = 15) whereas 51.6% of the patients were male (N = 16). Average time between the onset of rash and biopsy was 18.8 days. DIF analysis showed immune deposits in 19.4% (N = 6) of the patients; whereas no immune deposits were detected in 80.6% (N = 25) of the patients. The most frequent final diagnosis was adverse cutaneous drug eruption followed by ABSDs.

Conclusions: Our findings suggest that DIF may be used in conjunction with clinical-pathologic and clinical findings to reveal the associated skin diseases in erythrodermic patients. Erythrodermic patients presenting with clinical findings of ABSD should be considered for DIF examination.
Introduction

Erythroderma (exfoliative dermatitis) is defined as widespread erythema and exfoliation involving more than 90% of body surface area [1]. Men seem to be more affected compared to women male-to-female ratio ranging from 1.5 to 2.8 [1-3]. Average age at the onset differs among various studies and reported to be 50.7 and 57 years in two recent reports respectively.3,4 Even though skin involvement is the predominant clinical picture of the condition, life-threatening systemic complications such as tachycardia, electrolyte imbalance, edema and unstable body temperature may accompany [3].

Erythroderma generally arises from the exacerbation and generalization of a pre-existing skin diseases, even though new-onset cutaneous eruptions such as adverse cutaneous drug eruptions (ACDE), psoriasis, systemic allergic contact dermatitis (SACD), autoimmune bullous skin diseases (ABSD) such as bullous pemphigoid, pemphigus foliaceus may also be the cause [3,4]. Identification of the associated cutaneous disease is not always that easy and requires longitudinal evaluation of the patient to reveal the underlying cause and manage the complications.

Histopathological examination of the lesional skin provides significant clues related to the etiology and thus may be the most fundamental evaluation to enlighten the pathogenesis of erythroderma [5]. Direct immunofluorescence (DIF), on the other hand, might prove to be quite useful in cases of ABSD and leukocytoclastic vasculitis as the suspected causes of exfoliative dermatitis by revealing the specific immune deposition pattern in the biopsies taken from the perilesional and lesional skin respectively [5,6].

In our study, we aimed to determine the diagnostic role of DIF in identifying the etiology of erythroderma and show the relationship between the presence of immune deposits and underlying diseases of exfoliative dermatitis.

Methods

The present study was a retrospective study conducted by review of electronic medical data records and histopathologic slide images belonging to 31 patients in a tertiary referral hospital between January 2014 and September 2020. Ethics committee approval was obtained (project number: GO 20/1099, decision number: 2020/19-45, decision date: November 17, 2020) and informed consent was taken from the participants for the study. All the patients were diagnosed as erythroderma and cutaneous biopsies were taken for histopathological examination and DIF analysis. Patients without histopathological and DIF examination were excluded from the study. For DIF assay, skin tissue samples were frozen in a cryostat and then sectioned with a thickness of 5 µm. Then, fluorescein-labeled antisera against human IgM (Dako, dilution ratio: 1/20-1/40), IgG (Bio SB, dilution ratio: 1/25-1/100), IgA (Dako, dilution ratio: 1/20-1/40) and C3 (Diagnostic BioSystems Inc., dilution ratio: 1/75-1/100) were applied to sections and incubated. Presence of any positive immunofluorescence staining with IgM, IgG, IgA and C3 antisera was evaluated under immunofluorescence microscopy. Sex, age, dermatologic examination findings, accompanying systemic symptoms, clinical pre-diagnoses, laboratory findings, elapsed time between the onset of the rash and biopsy procedure, histopathologic findings, presence of immune deposits in DIF analysis, final diagnosis, treatment given and were evaluated and recorded. The underlying etiologies of erythroderma were divided into 4 categories as follows: 'category 1 (ABSD)', 'category 2 (ACDE)', 'category 3 (vascular skin diseases)' and 'category 4 (miscellaneous other skin diseases) (Table 1). For cases with a final diagnosis of ACDE including drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, maculopapular drug eruption (MDE), Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum (SJS-TEN) and vasculitic drug eruption, the most probable inciting drug/drugs were determined and time between the onset of the erythroderma and first drug intake was also evaluated.

Statistics

Statistical analyses were performed with the IBM SPSS for Windows Version 22.0 and MS Excel. Categorical variables were given as frequencies and percentages. Numerical variables were summarized as mean ± standard deviation or median (minimum-maximum).

Results

Demographical, clinical, pathological characteristics; pre-diagnoses and final diagnoses of the all study subjects along with DIF findings and laboratory abnormalities are shown in Supplementary File 1.

The average age of the subjects was 54.6 ± 23 years (range: 3-86 years, median: 61 years). 48.4% of the patients were female (N = 15) whereas, 51.6 % of the patients were male (N = 16). All patients presented with erythema and scaling covering > 90% of body surface area, 48.4 % of the patients (N = 15) had also one or more mucosal area (oral, anogenital and ocular) involvement. All patients with SJS (N = 4), five patients with MDE, two patients with DRESS, one patient with bullous mycosis fungoides, one patient with pemphigus foliaceus and two patients with SACD had mucosal involvement. The most common clinical presentations of oral mucosal involvement were hemorrhagic-crusted plaques covering the lips, erosions on the buccal and palatal mucosa which were predominantly observed in cases with SJS. Mucopurulent conjunctivitis, eyelid margin ulceration...
and vulvovaginal/penile erosions were also present in patients with SJS. Patients with MDE, DRESS and SACD most commonly had superficial erosions on the lips as the mucosal manifestation. The most frequent systemic symptoms and signs associated with erythroderma were fever (67.7%, N = 21), followed by pruritus (38.7%, N = 12). Hypotension, pain, irritability, facial/peripheral edema, lymphadenopathy, malaise, arthralgia and myalgia were also present. 29% of the patients (N = 9) had eosinophilia (> 500/mm³ cells); other accompanying laboratory anomalies are shown in Supplementary Table 1. The average elapsed time between the onset of rash and performing the biopsy was 18.8 ± 28.3 days (range: 1-150 days). DIF analysis showed immune deposits in 19.4% (N = 6) of the patients; whereas no immune deposits were detected in 80.6% (N = 25) of the patients. The final diagnoses of the underlying cutaneous diseases were classified as ‘category 1 (ABSD)’, ‘category 2 (ACDE)’, ‘category 3 (vascular skin diseases)’ and ‘category 4 (miscellaneous)’. Category 1 consists of bullous pemphigoid, pemphigus foliaceus; category 2 consists of ACDEs including SJS/TEN spectrum, DRESS, MDE, AGEP (acute generalized exanthematous pustulosis), fixed drug eruption, vasculitic

### Table 1. Underlying etiologies of erythroderma and direct immunofluorescence findings.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients N (%)</th>
<th>Presence of any accompanying bulla, vesicle pustule, erosion, crusting or necrosis</th>
<th>Direct Immunofluorescence Findings</th>
<th>Total (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 (Autoimmune bullous skin disorders)</td>
<td></td>
<td></td>
<td></td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Bullous Pemphigoid</td>
<td>2 (2.9%)</td>
<td>Bulla, crusting and erosion</td>
<td>Linear IgG and C3 deposition at the dermoepidermal junction</td>
<td></td>
</tr>
<tr>
<td>Pemphigus Foliaceus</td>
<td>1 (1.4%)</td>
<td>Flaccid bulla, vesicle and crusting</td>
<td>Intercellular IgG deposition</td>
<td></td>
</tr>
<tr>
<td>Category 2 (Adverse Cutaneous Drug Eruptions)</td>
<td></td>
<td></td>
<td></td>
<td>20 (64.5%)</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis</td>
<td>4 (5.8%)</td>
<td>Erosion, crusting and Nikolsky (+) bulla</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Maculopapular drug eruption</td>
<td>10 (14.5%)</td>
<td>-</td>
<td>Only one patient had linear IgM, granular IgG and IgA deposition at the dermoepidermal junction</td>
<td></td>
</tr>
<tr>
<td>Drug rash with eosinophilia and systemic symptoms</td>
<td>3 (4.3%)</td>
<td>-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Vasculitic drug eruption</td>
<td>1 (1.4%)</td>
<td>-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Fixed drug eruption</td>
<td>1 (1.4%)</td>
<td>Bulla, erosion, crusting</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Acute generalized exanthematous pustulosis</td>
<td>1 (1.4%)</td>
<td>Pustule</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Category 3 (Vascular Skin Diseases)</td>
<td></td>
<td></td>
<td></td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Purpura Fulminans</td>
<td>1 (1.4%)</td>
<td>Hemorrhagic bulla, necrosis</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>1 (1.4%)</td>
<td>Hemorrhagic bulla, necrosis</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis</td>
<td>1 (1.4%)</td>
<td>-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Category 4 (Miscellaneous)</td>
<td></td>
<td></td>
<td></td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>1 (1.4%)</td>
<td>Bulla</td>
<td>Interrupted C3 deposition along dermal vessels and dermoepidermal junction</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1 (1.4%)</td>
<td>-</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Psoriasiform dermatitis (finally diagnosed as idiopathic erythroderma)</td>
<td>1 (1.4%)</td>
<td>Pustule</td>
<td>Linear C3 deposition at the basal membrane</td>
<td></td>
</tr>
<tr>
<td>Systemic allergic contact dermatitis</td>
<td>2 (2.9%)</td>
<td>-</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
drug eruption; category 3 encompasses purpura fulminans, antiphospholipid syndrome and leukocytoclastic vasculitis, whereas category 4 consists of miscellaneous causes of erythroderma including, bullous mycosis fungoides, SACD, psoriasis and psoriasiform dermatitis (Table 1). Patients in category 3 (purpura fulminans, antiphospholipid syndrome and leukocytoclastic vasculitis) were accepted to present an erythrodermic-purpuric form of the disease described, since >90% of the body surface area were covered with erythema accompanied by hemorrhagic bullae and ecchymotic plaque. The most frequent final clinical-pathological diagnosis was ACDE category (category 2) (64.5%, N = 20) followed by bullous pemphigoid (6.5%, N = 2) and SACD (6.5%, N = 2) (Table 1). The only patient diagnosed histopathologically with ‘psoriasiform dermatitis’ was accepted to have an idiopathic form of erythroderma. Clinical and histopathological pictures of erythrodermic patients with different underlying etiologies are shown in Figures 1-5. Presence of any accompanying pustule, bulla, vesicle, necrosis, erosion and crusting were also determined as the part of dermatological examination as shown in table 1. For the category 2, the mean elapsed time between the onset of the rash and most probable inciting drug intake was 14.6 ± 13.9 days (range: 0-42 days). The most common probable causes of erythroderma were antimicrobials (40%, N = 8), followed by allopurinol (20%, N = 4), phenytoin (15%, N = 3), hydroxychloroquine (10%, N = 2), intravenous contrast media (10%, N = 2), chemotherapy agents (10%, N = 2) and others (15%, N = 3). The sample tissue for DIF examination was taken from the intact skin just at the periphery of a bulla that had a pre-diagnosis of bullous pemphigoid or pemphigus foliaceus, whereas skin samples were obtained from a vesicle, bulla or pustule for the subjects who had pre-diagnosis of vasculitis or drug eruption. All 3 cases of erythrodermic patients in the category 1 diagnosed with either bullous pemphigoid (N = 2) or pemphigus foliaceus (N = 1), 1 patient from category 2 diagnosed with MDE and 2 cases from category 4 diagnosed with bullous mycosis fungoides and psoriasiform dermatitis, respectively, showed positive immunofluorescence in DIF assay. Two cases of bullous pemphigoid showed linear IgG and C3 deposition at the dermoepidermal junction (Figure 4), whereas intercellular IgG deposition was detected in pemphigus foliaceus.

Conclusions

To our knowledge, this is the first study which evaluates diagnostic significance of DIF examination in clarifying the etiopathogenesis of exfoliative dermatitis. Immunofluorescence microscopy is a well-developed, advanced technique which is utilized for the detection of tissue-fixed antibodies. For cutaneous disorders, DIF is used for designation of the antibodies bound to a specific antigen in the skin [7]. DIF assay simply involves the application of fluorescein-labeled secondary antibodies to a frozen section of sample tissue followed by examination of the issue for the deposition of immune reactants under immunofluorescence microscopy [7]. DIF is generally considered to be an auxiliary tool which aids

Figure 1. (A) Presentation of erythroderma in a patient diagnosed with mycosis fungoides widespread erythema and scaling. (B) Yellow/brown color change and subungal hyperkeratosis of the fingernails. (C) Diffuse dermo-epidermal atypical lymphoid infiltrate which shows epidermotropism (H&E, x200).
to reach the accurate diagnosis of various dermatologic disorders especially when supportive histopathological changes are minimal. In dermatology practice, incorporating DIF findings with routine pathological findings are particularly useful in the patients pre-diagnosed with ABSD, connective tissue diseases and cutaneous vasculitis [7]. A study by Buch et al showed that the sensitivity of DIF was 94.44% and 84% in the pemphigus vs bullous pemphigoid group respectively [8]. DIF was shown to have diagnostic significance in the classification of cutaneous small vessel vasculitides especially in IgA vasculitis and lupus vasculitis [9]. In erythrodermic patients, expeditious diagnosis of the underlying cause is the essential step which enables the accurate intervention.

In our study, we aimed to determine the diagnostic utility of DIF in patients with exfoliative dermatitis.

Erythroderma appears to affect men more than women even though in some studies no sex predilection is showed [3,10]. In line with the present data in the literature, our study also showed a slight male predominance with a male-to-female ratio of 1.07. The mean age of affect study subjects in our study was 54.6 ± 23 years (range: 3-86 years, median: 61 years). In a retrospective study of 49 erythrodermic patients, the average age was reported to be 50.7 ± 17.9 years which was in concordance with our findings [4]. As an acquired-adulthood disease, erythroderma may have various underlying etiologies or may be idiopathic in at least 25% of
dermatoses leading causes being psoriasis, eczema and atopic dermatitis, in contrast to our study [4,12,13]. In our retrospective study, we only included erythrodermic patients with available DIF examination results: this factor might explain the discrepancy between the results of our study and other ones. Our results show that skin samples for DIF examination were mostly taken from the patients with a suspected the cases [11]. In the present study, the most frequent underlying etiology of erythroderma was ACDE followed by ABSD, SACD, psoriasis and mycosis fungoides. In two patients with diagnoses of mycosis fungoides and psoriasis, generalization/ accentuation of the pre-existing dermatoses had evoked the erythrodermic status. In different studies, the most common diseases associated with erythroderma were pre-existing dermatoses leading causes being psoriasis, eczema and atopic dermatitis, in contrast to our study [4,12,13]. In our retrospective study, we only included erythrodermic patients with available DIF examination results: this factor might explain the discrepancy between the results of our study and other ones. Our results show that skin samples for DIF examination were mostly taken from the patients with a suspected
diagnosis of bullous/vesicular or vasculitic skin diseases such as bullous pemphigoid, SJS, AGEP, FDE and leukocytoclastic vasculitis etc. So we most likely missed other causes of erythroderma for which DIF analysis was not performed in our center, which could be considered as a selection bias which is the limitation of our study.

In ACDE category, the most common causes of cutaneous eruption were antimicrobials followed by allopurinol, phenytoin, hydroxychloroquine, intravenous contrast media, chemotherapy agents and others. In concordance with our results, anticonvulsants, beta-lactams, allopurinol, rifampicin, trimethoprim-sulfamethoxazole and non-steroidal anti-inflammatory drugs are reported to be the leading causes of acquired erythroderma in multiple studies [4,13]. Only one patient in the ACDE group with a diagnosis of MDE showed deposits of linear IgM, granular IgG and IgA deposition at the dermo-epidermal junction. We believe that this immunoreactant deposition which was observed only in one patient was most likely non-specific. Duhra et al reported a case of paracetamol-induced fixed drug eruption with intercellular deposition of IgG and C3 in the lesional skin and suggested that immunoreactant deposition only in the affected skin might play a role in the recurrence of the lesions at the same site after a particular drug intake [14].

We want to underline the fact that MDE is a common cause of erythroderma and negative DIF examination favors the diagnosis of MDE, when ABSDs, fixed drug eruption and drug-induced vasculitis. In addition, two cases of TEN were shown to exhibit diffuse homogeneous deposits of IgM, IgA, IgG, C3c and C1q in the mid-epidermis of perilesional skin which was linked to the capacity of necrotic keratinocytes to absorb immunoreactants [15]. Diffuse intraepidermal deposition of immune deposits was thought to favor the early diagnosis of TEN [15]. In contrast with this report, we did not observe any immune deposition in 4 patients with a final diagnosis of SJS-TEN.

Overall, 6 (19.4%) patients showed immune deposition in DIF evaluation. All 3 cases of erythrodermic patients diagnosed with ABSDs had positive immunofluorescence in DIF assay. One patient was diagnosed to have pemphigus foliaceus; whereas the final diagnosis for the 2 patients was bullous pemphigoid. One patient diagnosed with MDE and two cases diagnosed with bullous mycosis fungoides and psoriasiform dermatitis, respectively showed positive immunofluorescence in DIF assay. Grekin et al reported 2 cases of erythrodermic psoriasiform pemphigus foliaceus which showed intercellular IgG deposition in DIF examination just like our study subject [16]. Our patient had presented with erythroderma accompanied by thick/adherent scales, superficial erosions and scattered hemorrhagic crusts resembling seborrheic dermatitis and SJS. Histopathological examination showed sub-corneal/intra-granular blister formation with neutrophils and few acantholytic cells which was compatible with pemphigus foliaceus (Figure 5). With the aid of DIF examination which revealed intercellular IgG deposition, the diagnosis of pemphigus foliaceus was confirmed. On the other hand Joly et al reported three black African men diagnosed with lichenoid erythrodermic bullous pemphigoid [17]. In these patients, histopathological examination showed subepidermal bulla with lichenoid infiltrate along with linear deposits of C3 along the basal membrane. Two erythrodermic patients in our study presented with widespread intact/flaccid bullae, erosion and crust formation. Histopathological examination revealed sub-epidermal bulla, basal vacuolar degeneration and eosinophil-rich infiltrate. With the help of DIF analysis which detected linear deposits of IgG and C3 along the dermo-epidermal junction; the final diagnosis was bullous pemphigoid; the etiology of exfoliative dermatitis was unraveled.

In the category 4, the study subject with a final diagnosis of bullous MF showed interrupted C3 deposition along dermal vessels and dermoepidermal junction in the perilesional skin, whereas the case with the histopathological diagnosis of psoriasisform dermatitis and final clinical diagnosis of idio-pathic erythroderma showed linear C3 deposition at the basal membrane in the perilesional skin. We believe that these C3 deposition are non-specific, thus does not seem to carry any diagnostic significance as reported in a study by Leibold et al [18]. In this study, 41 non-lesional, sun-exposed skin samples obtained from Mohs surgery sites, 21 specimens demonstrated interrupted, weak linear or granular staining with IgM, IgG, IgA, Clq and C3 antisa [18]. On the other hand, the two other patients with final diagnoses of leukocytoclastic vasculitis and vasculitis drug eruption did not show any immune deposition which might be linked to the long elapsed time between the onset of rash and biopsy (14 days) for both cases. DIF analysis is suggested to be performed within the first 24 hours to yield the best result [19]. Immunoreactants can not be shown efficiently 24-48 hours after the lesion formation.

Even though our study has limitations, in that it was a retrospective study and only small number of erythrodermic patients who had undergone both histopathological examination and DIF analysis were included, we would like to underline that DIF assay may be used as an auxiliary tool in enlightening etiopathogenesis of exfoliative dermatitis.

References


COVID-19 Knowledge in Patients with Psoriasis Receiving Systemic Therapy: a Questionnaire Study

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Key words: COVID-19, coronavirus, pandemic, psoriasis

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ABSTRACT

Introduction: Little is known about the impact of patient behavior on the treatment of psoriasis in the COVID-19 pandemic.

Objectives: We aimed to investigate the COVID-19 knowledge of the patients with psoriasis receiving systemic therapy in the pandemic.

Methods: The patients who received systemic treatment for psoriasis presented to our dermatology outpatient clinic were enrolled in the study. A questionnaire measuring the level of knowledge about COVID-19 and psoriasis was administered to patients. Demographics and disease characteristics of patients were recorded.

Results: A total of 183 patients with psoriasis were enrolled in the study. Of the patients, 33.9% thought that psoriasis exposes them to a risk of getting COVID-19, 30.6% declared that psoriasis treatment exposes them to a risk of getting COVID-19, and 59.6% were worried about getting COVID-19. The treatment discontinuation rate was 42.1%. The patients with high scholar level showed more anxiety and discontinued their treatment.

Conclusions: The patients with psoriasis did not have adequate knowledge of the effect of both psoriasis itself and its treatment on COVID-19 during the pandemic. The patients on biologic therapy tend to discontinue their treatment based upon the physician’s recommendation, whereas those on conventional therapy mostly on their own will. Clinicians should inform patients about current evidence of COVID-19 and psoriasis.
Introduction

Psoriasis is a chronic, immune-mediated disease that waxes and wanes with flareups. Most of the systemic therapies for psoriasis that are frequently used have immunosuppressive properties [1]. Since the World Health Organization (WHO) pronounced the COVID-19 (Coronavirus disease 2019) pandemic on March 11, 2020, there have been health service disruptions in the follow-up of chronic diseases such as psoriasis. Transformation of many hospitals into a COVID-19 center during the pandemic, reassignment of health workers to COVID-19 services resulted in disruptions in treatment for chronic diseases [2]. Psoriasis patients faced difficulties in accessing to medical care and routine follow-ups. Besides, it is not difficult to guess that patients with psoriasis who are taking particularly certain systemic medications that affect the immune system might have concerns about getting infected during the pandemic [3]. It has been observed that some patients on systemic therapy discontinued their treatment because of the fear of getting infected by COVID-19 [4]. However, there are few data showing how patients with psoriasis receiving systemic treatment are affected by pandemic and which way they prefer in their treatment decision making for psoriasis.

Objectives

We aimed to investigate the COVID-19 knowledge, attitude, and practice of the patients with psoriasis receiving systemic therapy in the COVID-19 pandemic.

Methods

The study was designed as a descriptive cross-sectional study. The psoriasis patients receiving systemic therapy presented to the dermatology outpatient clinic of our hospital between March 2020 and June 2021 were enrolled in the study. A questionnaire consisting of 12 questions measuring the level of knowledge about COVID-19 and their treatment for psoriasis was administered to patients giving verbal consent (Table 2). Sociodemographic (age, gender, education level, working status) and disease characteristics (duration, PASI (Psoriasis Area Severity Index), DLQI (Dermatology Life Quality Index), joint involvement, type of treatment) of the patients were recorded.

It was investigated whether there was any effect of patients’ characteristics (gender, education level, working status, PASI, DLQI, joint involvement, and type of treatment) on COVID-19 knowledge. Education level was divided into two groups as: low scholarly (primary + middle school) and high scholarly (high school + university). All patients were divided into two groups based on PASI scores. The patients whose score less than 10 was classified as mild psoriasis, and those with a score greater than 10 was classified as severe psoriasis. This was also carried out for DLQI scores. Types of psoriasis therapy were divided into conventional and biological treatments.

Approval for the study was obtained from the local ethics committee (Decision number 2020/111; 07/22/2020). All participants information was kept confidential and was used only for research purposes.

Statistical Analysis

Statistical analyses were performed using SPSS software (Version 22.0, IBM Corp). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test with Lilliefors significance correction) to determine whether they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables, medians, and minimum-maximum values for the non-normally distributed variables. The Chi-square test or Fisher exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups. A P of less than 0.05 was considered to show a statistically significant result.

Results

A total of 183 patients were included in the study. Ninety-one of all patients were female (49.7%) and 111 were male (50.3%). The mean age of all patients was 45.85 ± 14.13 years (Table 1). Demographic and disease characteristics of the patients are shown in Table 1. All patients completed the questionnaires (COVID-19 and DLQI). The distribution of the answers given by the patients to the questionnaire is shown in Table 2.

A small number of statistically significant differences were found in the analysis of the effect of patients characteristics (gender, education level, working status, PASI, DLQI, joint involvement, and type of treatment) on COVID-19 knowledge. Statistically significant differences between the groups in terms of the answers to the questionnaire are summarized in Table 3.

No statistically significant difference was found between those who work and those who do not in terms of having concerns about contracting COVID-19. No statistically significant difference was found between certain groups in terms of answers to questions 4, 7, 8, 9.

While most of the patients on biologic therapy discontinued their treatment based upon physician recommendation, those on conventional therapy made the decision mostly on their own will (Table 3). Secukinumab and methotrexate were the most frequently discontinued drugs in all patients (Table 4).
### Table 1. Demographic and clinical characteristics of the patients (N = 183).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>91 (49.7%)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>92 (50.3%)</td>
</tr>
<tr>
<td>Age (year), mean ± SD</td>
<td>45.85±14.13</td>
</tr>
<tr>
<td>Education level, N (%)</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>71 (38.8%)</td>
</tr>
<tr>
<td>Middle school</td>
<td>27 (14.8%)</td>
</tr>
<tr>
<td>High school</td>
<td>43 (23.5%)</td>
</tr>
<tr>
<td>University</td>
<td>42 (23%)</td>
</tr>
<tr>
<td>Employment status, N (%)</td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>94 (51.4%)</td>
</tr>
<tr>
<td>Nonworking</td>
<td>89 (48.6%)</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
</tr>
<tr>
<td>Duration of psoriasis (year), mean ± SD</td>
<td>13.32±9.41</td>
</tr>
<tr>
<td>Psoriatic arthritis, N (%)</td>
<td>46 (25.1%)</td>
</tr>
<tr>
<td>PASI, median (min-max)</td>
<td>4.5 (0-35.3)</td>
</tr>
<tr>
<td>DLQI, median (min-max)</td>
<td>14 (2-36)</td>
</tr>
<tr>
<td>Conventional therapies, N (%)</td>
<td></td>
</tr>
<tr>
<td>Acitretin</td>
<td>20 (10.9%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>83 (45.4%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>9 (4.9%)</td>
</tr>
<tr>
<td>Biologic therapies, N (%)</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>6 (3.3%)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12 (6.6%)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>17 (9.3%)</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>17 (9.3%)</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>17 (9.3%)</td>
</tr>
</tbody>
</table>

DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index; SD = standard deviation.

### Table 2. Distribution of answers given by patients to the questionnaire.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
<th>Patient, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you think having psoriasis put you at risk for COVID-19?</td>
<td>Yes</td>
<td>62 (33.9%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>90 (49.2%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>31 (16.9%)</td>
</tr>
<tr>
<td>2. Do you think psoriasis treatment put you at risk for COVID-19?</td>
<td>Yes</td>
<td>56 (30.6%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>82 (44.8%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>45 (24.6%)</td>
</tr>
<tr>
<td>3. Do you have any concern that you may contract COVID-19?</td>
<td>Yes</td>
<td>109 (59.6%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>74 (40.4%)</td>
</tr>
<tr>
<td>4. Where would you like to have your psoriasis treatment?</td>
<td>Home</td>
<td>120 (65.6%)</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>42 (23%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>21 (11.5%)</td>
</tr>
<tr>
<td>5. Do you think going to the hospital put you at increased risk of con-</td>
<td>Yes</td>
<td>123 (67.2%)</td>
</tr>
<tr>
<td>contracting COVID-19?</td>
<td>No</td>
<td>44 (24%)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>16 (8.7%)</td>
</tr>
</tbody>
</table>

Table 1 continues
Table 2. Distribution of answers given by patients to the questionnaire. *(continued)*

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
<th>Patient, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Has anyone in your family or friends had COVID-19?</td>
<td>Yes</td>
<td>30 (16.4)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>144 (78.7)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Contact</td>
<td>16 (8.7)</td>
</tr>
<tr>
<td></td>
<td>All (Respiratory+ Contact)</td>
<td>54 (29.5)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>8. What are the symptoms of COVID-19?</td>
<td>Fever</td>
<td>154 (84.2)</td>
</tr>
<tr>
<td></td>
<td>Sore throat</td>
<td>121 (66.1)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>127 (69.4)</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>113 (61.7)</td>
</tr>
<tr>
<td></td>
<td>Loss of smell</td>
<td>108 (59)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>97 (53)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>89 (48.6)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td>9. Which symptom(s) do you have make you think that you might have COVID-19 and seek medical attention?</td>
<td>Fever</td>
<td>64 (35)</td>
</tr>
<tr>
<td></td>
<td>Sore throat</td>
<td>29 (15.8)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>37 (20.2)</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>26 (14.2)</td>
</tr>
<tr>
<td></td>
<td>Loss of smell</td>
<td>19 (10.4)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>85 (46.4)</td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>6 (3.3)</td>
</tr>
<tr>
<td>10. Has your psoriasis treatment been discontinued during the pandemic?</td>
<td>Yes</td>
<td>77 (42.1)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>106 (57.9)</td>
</tr>
<tr>
<td>11. What was the reason for discontinuation of your treatment?</td>
<td>On my own will (patient)</td>
<td>35 (19.1)</td>
</tr>
<tr>
<td></td>
<td>Physicianrecommendation</td>
<td>40 (21.9)</td>
</tr>
<tr>
<td></td>
<td>Adverse effect</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>12. How long have you been without treatment?</td>
<td>One week</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Two weeks</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Three weeks</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Four weeks</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Eight weeks</td>
<td>15 (8.2)</td>
</tr>
<tr>
<td></td>
<td>Twelve weeks</td>
<td>36 (19.7)</td>
</tr>
<tr>
<td></td>
<td>Over twelve weeks</td>
<td>18 (9.8)</td>
</tr>
</tbody>
</table>

The most common duration that patients remain without treatment was 12 weeks, followed by over 12 weeks, 8 weeks, and 4 weeks (Table 5). No statistically significant difference was found between the medications in terms of duration of treatment discontinuation.

Conclusions

Since the beginning of the pandemic, the ability of health systems to manage chronic diseases has been impacted. Many hospitals in our country have been transformed into COVID-19 centers, health workers have been reassigned to COVID-19 services, and it has been aimed to reduce the admission of patients without urgent conditions to health institutions as much as possible. Therefore, there were health service disruptions in the follow-up of chronic diseases that require regular follow-up, such as psoriasis. In addition to pandemic measures and restrictions, many psoriasis patients discontinued their ongoing treatments or applied their treatments improperly due to the fear of getting infected. Various
### Table 3. Comparison of certain groups in terms of the answers to the questionnaire.

<table>
<thead>
<tr>
<th>Answers</th>
<th>Groups</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: Yes, having psoriasis put me at risk for COVID-19.</td>
<td>Mild psoriasis (PASI &lt; 10)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Severe psoriasis (PASI &gt; 10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis (-)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis (+)</td>
<td>0.01</td>
</tr>
<tr>
<td>Q2: Yes, psoriasis treatment put me at risk for COVID-19</td>
<td>Mild psoriasis (PASI &lt; 10)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Severe psoriasis (PASI &gt; 10)</td>
<td></td>
</tr>
<tr>
<td>Q2: No, I don’t think psoriasis treatment put me at risk for COVID-19</td>
<td>Severe psoriasis (DLQI &gt; 10)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Mild psoriasis (DLQI &lt; 10)</td>
<td></td>
</tr>
<tr>
<td>Q3. Yes, I have concerns about contracting COVID-19.</td>
<td>High scholarly</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Low scholarly</td>
<td></td>
</tr>
<tr>
<td>Q5. Yes, going to the hospital put me at increased risk of contracting</td>
<td>Female</td>
<td>0.03</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Q6. Yes, some of my family and friends have had COVID-19.</td>
<td>Severe psoriasis (DLQI &gt; 10)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Mild psoriasis (DLQI &lt; 10)</td>
<td></td>
</tr>
<tr>
<td>Q10. Yes, my psoriasis treatment has discontinued during the pandemic.</td>
<td>Biological treatment</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Conventional treatment</td>
<td></td>
</tr>
<tr>
<td>Q12. I discontinued treatment.</td>
<td>Conventional treatment</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Biological treatment</td>
<td></td>
</tr>
<tr>
<td>Q12. My doctor recommended that I stop treatment</td>
<td>Biological treatment</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Conventional treatment</td>
<td></td>
</tr>
</tbody>
</table>

The group in which a statistically significant difference was found in favor of itself is shown in bold.

DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index.

### Table 4. Distribution of the reasons for treatment discontinuation according to medications.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patient will</th>
<th>Physician recommendation</th>
<th>Adverse effect</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>19</td>
<td>9</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Conventional (Total)</td>
<td>23</td>
<td>14</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Biological (Total)</td>
<td>12</td>
<td>26</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>40</td>
<td>2</td>
<td>77</td>
</tr>
</tbody>
</table>

studies on psoriasis and COVID-19 are available in the literature [5-7]. These studies primarily focus on the management of psoriasis during the pandemic, and the effects of psoriatic disease itself and systemic treatments on COVID-19. There are few studies on the knowledge of psoriasis patients about COVID-19. In this study, we aimed to investigate the COVID-19 knowledge of the patients with psoriasis and how they address their psoriasis treatment during the pandemic. In the present study, 33.9% of the patients stated that psoriasis exposes them to a risk of getting COVID-19, whereas 49.2% responded that there was no risk, and 16.9% did not know. In addition, mostly patients with mild psoriasis (PASI <10 and without arthritis) declared that psoriasis exposes them to a risk of getting COVID-19. In a study including psoriasis (N = 51), atopic dermatitis (N = 22), and hidradenitis suppurativa (N = 25) patients, 28.6% patients thought that...
their disease expose them to a moderate-to-severe risk to contract COVID-19 [4]. It is not exactly known that the effects of psoriasis on contracting COVID-19. However, existing literature generally suggest that psoriasis patients have similar rates of COVID-19 infection as the general population [8].

In our study, 30.6% of the patients declared that psoriasis treatment exposes them to a risk of getting COVID-19, whereas 44.8% responded that there was no risk, and 24.6% did not know. Patients on conventional therapies were more than those on biologics among the patients who thought that psoriasis treatments do not expose them to a risk of contracting COVID-19. Similarly, patients with high DLQI (> 10) were more than those with low DLQI (< 10) among the patients who thought that psoriasis treatments do not expose them to a risk of contracting COVID-19. However, patients with low PASI (< 10) were more than those with high PASI (> 10) among the patients who thought that psoriasis treatments expose them to a risk. Bragazzi et al. reported that 8.1% of patients thought that biologics expose them to a risk to contract COVID-19 [4]. In our study, this rate was 13.1%. It remains unclear if treatments for psoriasis affect the risk of contracting COVID-19. Based on the available evidence, treatments for psoriasis do not meaningfully alter the risk of contracting COVID-19 [8].

Our patients had not adequate knowledge of the effect of both psoriasis itself and its treatment on COVID-19 to cope with psoriasis during the pandemic. Doctors are the most reliable source of health information for patients. In addition to the fact that doctor-patient interactions have been negatively impacted in the pandemic, the patients may not have requested information about COVID-19 from their physicians and/or the physicians may not have provided adequate information.

Thirty out of 183 patients had a history of COVID-19 in the family. A statistically significant difference was found between patients with severe and mild psoriasis in terms of having a family history of COVID-19. The patients with severe psoriasis may have avoided seeking medical attention because of increased anxiety since their relatives had COVID-19. Further investigation is needed on this issue.

In our study, 59.5% of the patients were worried about contracting COVID-19. Bragazzi et al. reported that this rate was 79.6% [4]. The relatively low rate in our study may be related to the limited knowledge of our patients about COVID-19. Further, patients with high scholarity level were more than those with low scholarity level among the patients who have concern about getting COVID-19 (P = 0.01). It seems that the increase in knowledge affects attitude. The patients with high scholarity may be looking up more information on COVID-19.

In our study, 65.6% of the patients declared that they would like to have their psoriasis treatment at home, whereas 23% prefer the hospital, and 11.5% did not know. In addition, 67.2% of patients stated that going to the hospital put them at increased risk of contracting COVID-19, 24% responded that there was no risk, and 8.7% did not know. It may be related that the patients who have inadequate knowledge of COVID-19 and the low number of people around them who had COVID-19 (16.4%).

Most of our patients had adequate knowledge and awareness about the symptoms of COVID-19 and how it transmits (Table 2). This is most likely related that there has been a lot of easy-to-read information sharing on COVID-19 everywhere since the beginning of the pandemic.

The treatment discontinuation rate was 42.1% and physician recommendation was the most common reason of the treatment discontinuation in our study (Table 2). In our clinic, we tried to reach out to all our patients receiving immunosuppressive drugs at the beginning of the pandemic. Despite the lack of information on how exactly

<table>
<thead>
<tr>
<th>Drug</th>
<th>1 week</th>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>&gt; 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Conventional (Total)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Biological (Total)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>15</td>
<td>36</td>
<td>18</td>
</tr>
</tbody>
</table>
immunosuppressive drugs should be used in the treatment of psoriasis in the early days of the pandemic, every patient who we reached out was evaluated for the risk: benefit ratio of immunosuppressive treatment. In this way, shared decision-making between clinician and patient was carried out. The uncertainty in the early days of the pandemic may have led both physicians and patients to be more cautious. This may have affected the treatment discontinuation rate in our study. In addition, while most of the patients on biologic therapy discontinued their treatment based upon physician’s recommendation, those on conventional therapy made the decision mostly on their own will (Table 3). Pre-treatment procedures are often required before starting treatment with biologics. So, patients with psoriasis receiving biologics could have more contact with physicians than those on conventional therapy. This opportunity may have provided an effective doctor-patient communication. In this way, our patients receiving biologics may have been more informed on their health issues than those receiving conventional therapy.

It appears that psoriasis patients with low scholarly level discontinued their treatment based upon the physician’s recommendation, those with high scholarly level made the decision mostly on their own will. The patients with high scholarly were more than those with low scholarly among the patients who have concern about getting COVID-19. This may have caused them to discontinue their treatment. Also, it may be related that patients with low scholarly tend to leave decision-making to physician in the use of systemic therapies in the pandemic.

This study is not without any limitation. It is a single-center study including relatively a low number of patients.

Patients with psoriasis may not have adequate knowledge of the effect of both psoriasis itself and its treatment on COVID-19 during the pandemic. The present study reveals that psoriasis patients with high scholarly level can show more anxiety and discontinue their treatment. Patients with psoriasis on biologic therapy tend to discontinue their treatment based upon the physician recommendation, whereas those on conventional therapy mostly on their own will. Clinicians should inform patients about current evidence of psoriasis and COVID-19.

References


Granuloma Annulare: a Case-control Study of Possible Associated Diseases

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Key words: granuloma annulare, diabetes, hypothyroidism, hypercholesterolemia


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ABSTRACT

Introduction: Granuloma annulare (GA) has been reported as associated with multiple diseases, mainly diabetes mellitus (DM), thyroid diseases, and dyslipidemia. However, the high prevalence of some of these illnesses makes it difficult to assess whether the association is real or fortuitous.

Objectives: Our objective was to analyze the clinical features of GA patients and the possible associations.

Methods: This is a retrospective observational study of 225 patients with biopsy-proven GA diagnosed between 2009 and 2019 in a referral university hospital in Barcelona, Spain. Clinical charts were reviewed to obtain clinical data. As a control group we used a random list of 225 patients diagnosed in the hospital traumatology department in the same period, matched by age and sex.

Results: Diabetes was diagnosed in 40 GA patients (18%) (34 in the control group, 15%) and hypothyroidism in 33 (15%) (22 in the control group 9.8%); the differences were not significant. We also did not detect any association with uveitis, sarcoidosis, necrobiosis lipoidica, Sweet syndrome, HIV infection, hepatitis B, or hematological malignancies. We only detected a possible association with hepatitis C (6 GA patients, 2.7%, versus 0 controls, P = 0.03), and hypercholesterolemia (108 GA patients, 48%, versus 79 controls, 35%, P = 0.007).

Conclusions: The possible pathogenic explanations for the association with hepatitis C and hypercholesterolemia seem unlikely. We consider that the association of GA with other diseases, including hypercholesterolemia and hepatitis C, is doubtful and that there is no justification rule out possible associated diseases in patients with GA.
Introduction

Granuloma annulare (GA) is a disease of the skin and subcutaneous tissue of unknown etiology characterized by annular plaques, papules, or nodules containing foci of altered collagen surrounded by histiocytes and lymphocytes. It is a relatively frequent entity with a benign clinical course that in most cases does not require treatment [1,2]. It has been reported as associated with multiple diseases, mainly diabetes mellitus (DM), thyroid diseases, and dyslipidemia. However, the high frequency of some of these illnesses in the general population makes it difficult to assess whether the association is real or fortuitous [1,3]. Although there are multiple studies on the subject, to date no adequately controlled studies have been performed [1].

Objectives

Our objective was to review a series of patients with GA diagnosed histologically in the last 10 years in our hospital in order to analyse their clinical features and the possible association with other diseases.

Methods

We carried out a retrospective observational study of a series of 225 patients clinically and histologically diagnosed with GA between 2009 and 2019 at Bellvitge Hospital in Barcelona. This is a tertiary referral university hospital that provides healthcare to a population of approximately 1 million people. Cases registered as GA in the database of the pathology department were reviewed. The diagnostic criteria were the presence of palisaded granulomas with mucin deposition inside the granuloma.

Cases with lesions limited to the limbs or trunk were classified as localized GA, while those with lesions on the trunk and extremities (upper, lower, or both) were considered generalized GA [4]. Cases with epidermal perforation on biopsy were diagnosed with perforating GA, and the cases with lesions limited to the hypodermis were classified as subcutaneous GA. Finally, cases with large erythematous or brownish smooth-surface macules on the trunk and extremities without induration and with a histological pattern of interstitial GA were classified as patch GA [5]. The medical records of the patients were retrospectively reviewed to obtain the following data: race, sex, age of the patients at the time of diagnosis, date of diagnosis, evolution time of the lesions, number of lesions, location, clinical form of GA (localized, generalized, subcutaneous, perforating, and patch-type), duration of the lesions, presence of DM, hypercholesterolemia, thyroid diseases, uveitis, HIV, hepatitis B, hepatitis C, hematological neoplasms, sarcoidosis, Sweet syndrome, and association with drug treatments. The treatments carried out and the follow-up time of the patients were also recorded.

Control Group

For a control group, a random list of patients diagnosed in our hospital traumatology department between 2009 and 2019, was used. For each case, a control of the same age and sex was randomly taken. For case and control, the clinical history of the patients in the public health system was accessed to record whether they were diagnosed with the above cited entities by their primary care physician before or during the year of the diagnosis of GA or of the visit to traumatology. All controls were Caucasian except for 1 male and 3 females of South American descent.

Statistical Analysis

Data were explored with the SPSS 17.0 statistical package for Windows. The proportions of cases with the possible associated diseases in the group of patients with GA and in the control group were compared using Fisher exact test. The possible relationships between the different variables analyzed were also investigated. Categorical variables were compared using Fisher exact test. Continuous variables were compared using Student t test when the normality of the data distribution was confirmed. Otherwise, the Mann-Whitney U test was performed. Statistical significance was established at a value of P < 0.05.

Results

These were 225 patients, 155 women (69%) and 70 men (31%), aged between 4 and 91 years (mean age 54.91 years, standard deviation [SD] 16.296). At the time of diagnosis, 155 patients were older than 50 years (69%). All patients with GA were Caucasian except for 2 women of South American descent. GA lesions involved the upper extremities in 150 patients (hands 69, elbows 64, rest of the upper extremities 78), the lower extremities in 92 (feet 15, knees 22, rest of the lower extremities 78), the trunk in 82 (anterior part of the trunk 70, posterior part 40), and the head and neck region in 25 (19 neck, 6 face). Classic localized GA was the most frequent form of GA (124 cases, 55%) followed by generalized GA (72 cases, 32%), patch-type GA (35 cases, 16%, some of them generalized), subcutaneous GA (6 cases 2.7%) and perforating GA (4, 1.8%). Among the 191 cases in which the extent of the lesions could be assessed, 117 had fewer than 10 lesions and 74 had more than 10 lesions. The time of evolution of the lesions at diagnosis was 11.74 months, SD 19.284. The duration of the lesions until healing or the last follow-up was established in 112 cases,
ranging between 1 and 240 months (mean 31.46 months, SD 39.921). In 68 of these 112 cases, the lesions persisted for less than 2 years (61%). In 23 patients the lesions were recurrent. The follow-up time of the patients ranged between 1 and 120 months, with a mean follow-up of 21.83 months, SD 27.851. The prescribed treatments were: no treatment in 46 patients, topical corticosteroids in 163, systemic corticosteroids in 30, topical tacrolimus in 22, antimalarials in 14, intralesional corticosteroid infiltrations in 8, pentoxifylline in 8, dapsone in 2, tetracyclines in 2, and isotretinoin in 1. Twenty patients received 3 or more treatments.

Table 1 shows the clinical features of the lesions according to the sex of the patients. Table 2 shows the diseases detected in the cases and in the controls.

In the analysis of the possible relationships between the variables analyzed, the following relationships were significant: male patients more frequently had hand lesions than female patients (P = 0.017); female patients had lower limb lesions more frequently than male patients (P = 0.002); patients with patch GA more frequently had lesions on the trunk (P = 0.020) and lower limbs (P = 0.013) than the rest of the patients; and finally, in a higher proportion of patients with less than 10 lesions, the lesions involved the upper extremities compared to the rest of the patients (P = 0.015).

Table 1. Clinical features according to the sex of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Female 155 (69%)</th>
<th>Male 70 (31%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.62 SD 16.041</td>
<td>55.54 SD 16.948</td>
</tr>
<tr>
<td>Evolution at diagnosis (months) 11.74 SD 19.284</td>
<td>12.56 SD 21.874</td>
<td>9.87 SD 11.236</td>
</tr>
<tr>
<td>Total duration (months) 31.36 SD 39.921</td>
<td>32.92 SD 44.453</td>
<td>27.94 SD 26.330</td>
</tr>
<tr>
<td>Upper limbs, N 150 (67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands 69</td>
<td>106/155 (68%)</td>
<td>44/70 (63%)</td>
</tr>
<tr>
<td>Elbows 64</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>Rest 78</td>
<td>53</td>
<td>11</td>
</tr>
<tr>
<td>Lower limbs, N 92 (41%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feet 15</td>
<td>75/155 (48%)</td>
<td>17/70 (24%)</td>
</tr>
<tr>
<td>Knees 22</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Rest 78</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Trunk, N 82 (36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior 70</td>
<td>59/155 (38%)</td>
<td>23/70 (33%)</td>
</tr>
<tr>
<td>Posterior 40</td>
<td>49</td>
<td>21</td>
</tr>
<tr>
<td>Head and neck, N 25 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck 19</td>
<td>14/155 (9%)</td>
<td>11/70 (16%)</td>
</tr>
<tr>
<td>Face 6</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Generalized, N 72 (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch, N 35 (16%)</td>
<td>54 (35%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Subcutaneous, N 6 (2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforating, N 4 (1.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 lesions, N 74/191 (39%)</td>
<td>55/132 (42%)</td>
<td>19/59 (32%)</td>
</tr>
</tbody>
</table>

SD = standard deviation.

Conclusions

Although the incidence of GA in the population is unknown, it is one of the most frequent chronic dermatological diseases. GA has been estimated to represent approximately 0.1–0.4% of dermatology outpatient visits in the United Kingdom [6] and 0.22-0.27% in the United States of America [7]. In our hospital we have not quantified the number of visits due to GA but the histological diagnosis of GA represents 0.97% of the skin biopsies.

According to the literature, GA occurs more frequently in the first 3 to 5 decades of life, with a ratio of women to men of around 1:2:1 [2]. In some series the percentage of women is higher, up to 85% [7], being 69% in our series (female / male ratio of 2.21 / 1). Regarding age, we had a higher mean age than in other series (55 years, with 155 cases over 50 years), probably due to the lack of pediatrics department in our hospital.

It is known that GA lesions are usually located in the extremities, especially the back of the hands and feet [2]. In our series, the upper extremities were affected in 150 patients (67%) and the lower extremities in 92 (41%), but the trunk was also frequently affected (82 cases, 36%). There are five common clinical variants of GA (localized, generalized, patch-type, subcutaneous, and perforating). According to the
60 cases of generalized GA did not detect significant differences with the control group (19% in the group with GA and 9.33% in the control group) [9]. For this reason, we consider it unlikely that GA is associated with malignant solid neoplasms and we did not investigate this possibility in the present study.

Diabetes mellitus (DM) is the disease most frequently analyzed as possibly being associated with GA. Some articles suggest that there is a putative association [3,10-12], especially with generalized GA [4], while other articles reject this [13-15]. The association with DM has been attributed to microvascular dysfunction induced by diabetes. In addition, as diabetes is associated with elevated inflammatory cytokines as well as T-cell and macrophage activation, it has been suggested that diabetes may act as risk factor for GA through dysregulated T-cell activity. In the present study, 40 of the 225 patients with GA (18%) were diabetic at diagnosis or had a diagnosis of DM in the subsequent 12 months, compared to 34 in the control group (15%), a difference that was not statistically significant. Among the 72 cases of generalized GA, the incidence of DM was similar (13/72, 18%) and the differences were therefore not significant either. There are also several studies that suggest a possible association with thyroid diseases, especially hypothyroidism [7,16]. As GA is considered an autoimmune disease, it has been suggested that the association of GA with autoimmune thyroidal diseases may be based on a common immunogenetic predisposition. In our study, 33 of our patients with GA (15%) were diagnosed with hypothyroidism compared to 22 in the control group (9.8%) and the difference was also not significant. Other diseases that have been reported

| Table 2. Diseases detected in cases and in controls. |
|-----------------|-----------------|-----------------|
| Age             | 54.91 SD 16.296 | 55.12 SD 16.321 |
| Sex (female/male), N | 155/70          | 155/70          |
| DM, N           | 40 (18%)        | 34 (15%)        |
| 1               | 3               | 2               |
| 2               | 37              | 32              |
| Hypothyroidism, N | 33 (15%)        | 22 (9.8%)       |
| Hypercholesterolemia, N | 108 (48%)   | 79 (35%)        | P = 0.007 |
| Hematologic neoplasms, N | 4 (1.8%)      | 1 (0.4%)        |
| HIV, N          | 1 (0.4%)        | 0               |
| Hepatitis B, N  | 3 (1.3%)        | 1 (0.4%)        |
| Hepatitis C, N  | 6 (2.7%)        | 0               | P = 0.030 |
| Sarcoïdosis, N  | 1 (0.4%)        | 0               |
| Necrobiosis lipoidica, N | 1 (0.4%)  | 0               |
| Uveitis, N      | 0               | 0               |
| Sweet syndrome, N | 0               | 0               |

DM = diabetes mellitus; SD = standard deviation.
with some frequency as being associated with GA are uveitis [17,18], sarcoidosis [19,20], necrobiosis lipoidica [21], and Sweet syndrome [22]. In the present study we did not detect a significant association with any of them. Regarding infections, possible associations with HIV infection, hepatitis B, and hepatitis C have been suggested [3]. We did not detect an association with HIV or hepatitis B, but 6 of our GA patients had positive serology for hepatitis C (2.7%) compared to none of the controls. Although the number of cases is limited, the differences were significant (P = 0.03). As a possible pathogenesis, it has been suggested that infection by hepatitis C virus may generate a cell-mediated immune response that induces the formation of granulomas, since the presence of epithelioid granulomas in the liver has been detected in 10% of patients with HCV-related cirrhosis [23]. In addition, in some patients with generalized GA and hepatitis C, resolution of cutaneous lesions has been reported after hepatitis treatment [23,24]. Our data suggest that although in some patients infection by hepatitis C virus may induce GA, this situation is extremely rare, and in most cases GA is not related to hepatitis C virus infection.

The most noteworthy of our results is that we detected a significantly higher incidence of hypercholesterolemia among patients with GA than among controls, 108 cases (48%) versus 79 cases (35%) (P = 0.007). The association of GA with dyslipidemia was detected in a previous study in which 80% of 140 patients with GA had dyslipidemia compared with 52% of the controls (P < 0.001) [25]. This survey also detected a significant association with the extent of the lesions and a higher prevalence of dyslipidemia in generalized GA. In contrast, in our series the comparison of the incidence of hypercholesterolemia between generalized and localized GA did not reveal significant differences. The pathogenic mechanisms that might explain the relationship between GA and hypercholesterolemia are unclear. Observations that support an association between GA and dyslipidemia include the presence of lipid droplets in a considerable proportion of GA biopsies [21,26], and the histological similarity of GA to eruptive xanthoma [27,28]. It has also been suggested that the association of GA with dyslipidemia may be due to inflammation caused by the granulomatous disease itself, since chronic inflammation in diseases with cytokine patterns similar to GA, such as lichen planus and psoriasis, can trigger dyslipidemia [29-31]. On the other hand, the presence of microangiopathy in GA similar to that observed in necrobiosis lipoidica suggests that the granulomatous process may be secondary to microvascular dysfunction as a result of hypercholesterolemia [32,33]. Healing of GA lesions after dyslipidemia treatment also lends support to a pathogenic relationship between the two entities [34]. However, these putative explanations are not widely accepted and some seem unlikely. The high incidence of hypercholesterolemia in the general population and the lack of uniformity in the diagnostic criteria for hypercholesterolemia make these results difficult to assess. For this reason, despite the significant differences in the proportion of patients diagnosed with hypercholesterolemia among those with GA compared to the control group in the present study, we consider a pathogenic relationship between both entities to be unlikely.

One limitation of our study is that it is a retrospective survey and some clinical data of the patients are not included in the medical records. Another limitation is that these are cases diagnosed by biopsy in a referral hospital without pediatrics department, so generalized cases may be overrepresented and the adult population may be overrepresented. As for the case-control study, the high frequency of some diseases in the general population makes it difficult to investigate a true relationship with GA.

In summary, our study did not detect an association between GA and pathologies such as DM and hypothyroidism. We only detected a significantly higher proportion of patients with hypercholesterolemia and hepatitis C than in the control group. However, the possible pathogenic explanations for this association seem unlikely. We feel that association with other diseases, including hypercholesterolemia and hepatitis C, is doubtful and that it is not justified to systematically rule out the existence of possible associated diseases in patients with GA.

References


Omalizumab for the Treatment of Chronic Spontaneous Urticaria: Association Between Body Mass Index and Outcome

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Key words: omalizumab, chronic spontaneous urticaria, BMI

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ABSTRACT

Introduction: Omalizumab has been recently registered as a third-line therapy for chronic spontaneous urticaria.

Objectives: In this study, we aimed to provide real life data by reporting our experience with omalizumab in the treatment of chronic spontaneous urticaria.

Methods: A retrospective data analysis was conducted on 40 patients affected by chronic spontaneous urticaria and treated with omalizumab at the Dermatology Unit of Padova University Hospital. Demographic, anthropometric, and clinical data have been collected.

Results: Overall, the majority of patients (23 patients, 57.5%) achieved complete recovery by taking omalizumab and 17.5% (7 patients) had a partial response. The majority of patients who did not have a response to omalizumab had a body mass index (BMI) > 25 kg/m².

Conclusions: Our study suggests that omalizumab is a safe and effective treatment for chronic spontaneous urticaria. We identified BMI as a critical biological factor that significantly impacts the outcomes of omalizumab treatment. Our findings also suggest a potential use of BMI as a predictive biomarker for omalizumab treatment. An up-dosing of omalizumab may be proposed in patients with high BMI to achieve a better control of the disease.
**Introduction**

Chronic spontaneous urticaria (CSU) is a common disease, however, epidemiological data currently available on CSU prevalence ranging from 0.02% to 1% in different studies [1,2]. It is clinically characterized by the recurrent appearance of itch, wheals and/or angioedema for more than 6 weeks in absence of a known trigger [3]. It is often a self-limiting disease lasting no more than 2-5 years; however in 20% of patients lasts for more than 5 years. Many factors may play a role in the pathogenesis of chronic idiopathic urticaria, including infections, diet, drugs, emotional factors, and stress [1,4]. Chronic spontaneous urticaria highly impacts quality of life of patients affected. Pruritus causes variable discomfort, as well as cutaneous wheals which may harm individual physical appearance and social life. The first line therapy for CSU consists in the use of non-sedating H1-antihistamines. If the response is inadequate after two weeks of treatment, increasing the antihistamine dosage up to four-fold is recommended as second-line therapy [2,4]. Omalizumab, a humanized anti-IgE monoclonal antibody, that was primarily approved for the treatment of moderate/severe asthma has been recently registered for CSU treatment as a third-line therapy [5-8].

**Objectives**

In this study, we aimed to provide real life data by reporting our experience with omalizumab in the treatment of CSU.

**Methods**

A retrospective data analysis was conducted on 40 patients affected by CSU and treated with omalizumab between 2016 and 2019 at the Dermatology Unit of Padova University Hospital.

All patients provided written informed consent. The patients included were aged over than 18 years with at least 6 months history of chronic idiopathic urticaria. The severity of the urticaria was assessed thanks to the Urticaria Activity Score (UAS) and established both daily and weekly (UAS7), based on the presence of wheals and itching.

All patients received a 300 mg subcutaneous injection of omalizumab every 4 weeks for at least 6 months. Once a month, follow-up visits were scheduled together with the omalizumab infusions. The following data were collected: birth date, sex, height, weight, date of urticaria diagnosis, severity of the disease, previous urticaria therapies, comorbidities, and concomitant medications. The body mass index (BMI) value was calculated (in kg/m²) to classify patients as underweight (BMI < 18.4 kg/m²), normal weight (18.5 kg/m² ≤ BMI ≤ 24.9 kg/m²), overweight (25 kg/m² ≤ BMI ≤ 29.9 kg/m²) and obese (BMI ≥ 30 kg/m²). The date of the first omalizumab administration, the number of therapy cycles and the date of the last infusion were recorded as well as any adverse events during or after omalizumab administration. The outcome of the treatment with omalizumab was evaluated based on the patient’s report, any objective improvement or worsening, and reduction of UAS7. UAS7=0 was considered as complete response, while a 90% reduction in UAS7 was considered as a partial response. Benefit achieved after a single course of omalizumab was considered a partial response.

**Results**

The study included 40 patients with the following demographic characteristics: 30 females (75%) and 10 males (25%), with a mean age of 49 years (range: 21-81 years). The minimum BMI detected was 17.8 kg/m², while the maximum was 34 kg/m², with an average value of 24.1 kg/m². The patients were divided in underweight, normal weight, overweight and obese (Table 1). The date of urticaria diagnosis was between 1994 and 2019. The mean age of patients at the time of the diagnosis was 45 years. All patients were affected by severe disease with UAS > 4 and UAS7 > 30 before starting treatment with omalizumab.

Medications used before omalizumab for the treatment of CSU included three main classes of drugs: antihistamines (85% of patients, mainly desloratadine), glucocorticoids (62.5% of patients, mostly prednisone) and immunosuppressants (27.5% of patients, primarily cyclosporine). Furthermore, 27.5% of patients followed a histamine-free diet, 10% of cases received a supplementation with nicotinamide, while 5% of patients were treated with UVB phototherapy. The majority of patients (80%) presented comorbidities including allergic rhinitis (20%), hypothyroidism (20%), nickel allergy (15%), grasses allergy (12.5%) and atopic dermatitis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Underweight</th>
<th>Normal Weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>2 (5%)</td>
<td>17 (42.5%)</td>
<td>7 (17.5%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>0</td>
<td>6 (15%)</td>
<td>4 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1. Classification of patients based on the BMI value according to the WHO: underweight (<18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²) and obese (>30 kg/m²)
(12.5%) were detected. Simultaneously to the omalizumab therapy, many patients have taken various therapies for both CSU and their concurrent diseases including antihistamines (60%), glucocorticoids (55%), levothyroxine (15%). In addition, 15% of patients continued to follow a histamine-free diet and 12.5% were taking nicotinamide.

Overall, 30 patients (75%) completed the entire course of omalizumab therapy, while 10 of them (25%) discontinued omalizumab due to acute side effects (discontinuation at the first dose, in 2 patients), other diseases (2 patients) or ineffectiveness (6 patients). Based on the results obtained, patients were classified into three categories: no response (10 cases, 25%), partial response (7 patients, 17.5%), complete response (23 patients, 57.5%) (Figure 1). The majority of patients who did not have a response to omalizumab had a BMI > 25 kg/m².

Binomial logistic regression enables us to determine which of our independent variables have statistically significant effect on outcome; considering age, sex and BMI as variables, emerged that BMI has a statistically significant effect (P = 0.042), and odds ratio < 1 indicates a positive predictive value of better response to therapy (Table 2).

Conclusions

In our cohort patients were predominantly female (M:F ratio was 1:3), according to the literature, which reports a prevalence of CSU two times higher among women than man. It may be explained by the role of autoimmunity in CSU

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![Figure 1](image-url)

**Figure 1.** Outcome of omalizumab treatment. Complete response: UAS7=0; Partial response: 90% reduction of UAS7 values; 25% of patients (10 patients) had no response; 17.5% of patients (7 patients) reported partial response, while 57.5% (23 patients) had a complete response to omalizumab.

**Table 2. Model coefficients – outcome**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Estimatea</th>
<th>SE</th>
<th>Z</th>
<th>P</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>3.8904</td>
<td>2.5292</td>
<td>1.538</td>
<td>0.124</td>
<td>48.930</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.2105</td>
<td>0.1037</td>
<td>-2.029</td>
<td>0.042</td>
<td>0.810</td>
</tr>
<tr>
<td>Age</td>
<td>0.0458</td>
<td>0.0315</td>
<td>1.452</td>
<td>0.147</td>
<td>1.047</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M – F</td>
<td>0.8918</td>
<td>1.0390</td>
<td>0.858</td>
<td>0.391</td>
<td>2.439</td>
</tr>
</tbody>
</table>

BMI = body mass index; F =female; M = male; SE = standard error.

*aEstimates represent the log odds of “Outcome = yes” versus “Outcome = no”
pathogenesis [3]. Patients aged from 21 to 81 years have been treated, showing omalizumab safety in all age groups, even in the elderly patients which may have comorbidities [9]. The average value of BMI was 24.1 kg/m², which belongs to the category of normal weight but with a tendency to overweight. Although the study population is not large, the distribution of BMI categories was overlapping to the percentage obtained by 2016 ISTAT on the entire Italian population. The most common diseases associated with CSU were hypothyroidism, hypertension, allergic rhinitis, nickel and grass allergy and atopic dermatitis. Several patients included in our case series were also affected by atopic dermatitis, vitiligo, psoriasis, alopecia, SLE, scleroderma, spondylarthritids and/or diabetes suggesting a potential role of autoimmunity.

Our patients continued their concomitant treatments during omalizumab cycles, including antihistamines (60% of patients) and low-dose oral corticosteroids (55% of patients) intake. In addition, 15% of patients continued to follow a histamine-free diet and 12.5% were taking nicotinamide. No pharmacological interactions were observed, confirming literature data [7,10].

Most of patients (57.5%) had a complete response. Moreover, considering partial responses and first cycle benefits, 30 out of 40 patients (75%) had at least a partial favorable response. Given the small number of subjects recruited a statistical analysis has not been performed, but a significant number of patients with a beneficial effect from the use of omalizumab has emerged. Concerning the occurrence of adverse reactions to omalizumab, only 2 cases out of 40 (5%) were reported. Specifically, a single case of angioedema and 1 case of respiratory crisis have been documented, leading to therapy discontinuation. Other reasons why patients interrupted omalizumab were ineffectiveness or the onset of disease that required hospitalization (breast cancer, atrial fibrillation, splenic aneurysm). The total number of patients who discontinued the first course of omalizumab was 10 (25%).

Recent findings have shown an increased prevalence of metabolic syndrome among patients with CSU, which is characterized by a pro-inflammatory state, increased oxidative stress and alterations in adipokine profile [11-13]. Interestingly, the majority of patients (7/10) who did not have a response to omalizumab had a high BMI (BMI > 25 kg/m²), suggesting the potential role of adipokines in mast cells activation leading to CSU worsening. However, the high body weight may also influence the pharmacokinetics of the drugs affecting the apparent volume of distribution of the drugs, as documented in other studies on biological treatments [13-15].

The recommended dose of omalizumab for the treatment of CSU is 300 mg every 4 weeks, but there is no recommendation for patients who do not benefit from this dose. While for patients affected by asthma the recommended dose of omalizumab changes according to the body weight of the patient, a fixed dose regimen is recommended for CSU regardless of the body weight and total IgE levels. In the recent years, there have been several studies on updosing of the drug, suggesting that the individualized approach for urticaria treatment with omalizumab is useful [16]. Patients with a higher BMI have been found to require higher doses to control the disease [17]. A step-wise approach starting from 450 mg and then updosing to 600 mg has been proposed if there is no response after 3 months of treatment in CSU patients [17]. Furthermore intervention on lifestyle through a combination of dietary changing and physical activity should be recommended in patients with high BMI.

Total IgE serum level do not justify an omalizumab dose changing however, it is a reliable biomarker predicting response to omalizumab in CSU since levels are significantly higher in responder than non-responder patients [18].

The main limitation of our study is the small number of patients included. Furthermore, all patients had a high UAS and some patients continued antihistamines and corticosteroids during omalizumab. We know that these may be confounding factors that may have influenced the outcome.

In conclusion, in this study we identified BMI as a critical biological factor that significantly impacts the outcomes of omalizumab treatment. Our findings also suggest a potential use of BMI as a predictive biomarker for omalizumab treatment. An up-dosing of omalizumab may be proposed in patients with high BMI to achieve a better control of the disease.

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Videodermoscopic Changes of the Hair in Vitiligo Lesions in Relation to Disease Duration

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Key words: vitiligo, videodermoscopy, hair changes, alopecia areata incognita


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ABSTRACT

Introduction: Vitiligo is an acquired disease of complex pathogenesis, in which the immunologic attack to the skin and hair follicle melanocytes leads to areas of depigmentation and leukotrichia, respectively.

Objectives: To study the dermoscopic features of the hair changes in vitiligo lesions in comparison to perilesional control areas and in relation to disease duration.

Methods: Forty-seven patients with both old and recent vitiligo lesions were included. Dermoscopic features of hair within the lesions were examined and compared to those in perilesional non depigmented skin of the same patient.

Results: Hair density (P < 0.001), terminal hair rate (P = 0.011), terminal to vellus hair ratio (P = 0.029) and mean hair shaft thickness (P = 0.031) were significantly decreased, whereas vellus hair rate (P = 0.011) was significantly increased in old vitiligo lesions compared to their respective control areas. The frequency of broken hair was significantly higher in old lesions (P < 0.001), while that of upright re-growing hair was significantly higher in recent lesions (P = 0.016).

Conclusions: Hair involvement in vitiligo lesions is not only limited to the development of leukotrichia. Other subtle changes in hair density, anagen and telogen hair rates, and mean hair thickness can be detected. These changes may serve as objective clues to the duration of the lesions.
### Introduction

Vitiligo is an acquired chronic depigmenting autoimmune disease of the skin and hair; in which progressive destruction of melanocytes occur. Loss of melanocytes from the epidermis is the cause of leukoderma, and if the process extends to involve the active bulbar melanocytes, leukotrichia will develop [1]. In addition to the characteristic skin involvement in vitiligo, other associated manifestations including ocular and audiological findings have been described [2-4].

Several theories have been put forward to explain the etiopathogenesis of vitiligo; among which autoimmunity is the leading one. The increased prevalence of several autoimmune diseases in vitiligo patients as well as their first degree relative has been reported, which suggests a general genetic predisposition to autoimmunity [4,5]. One of the commonly associated autoimmune diseases with vitiligo is alopecia areata (AA) [6]. Both diseases have common genetic risk factors and share certain similarities regarding their pathogenesis [7,8]. Several reports of colocalization of vitiligo and AA especially on the scalp exist in the literature [9-12], with skin biopsies exhibiting features of both diseases [12]. Moreover, relatively decreased hair density was previously reported in a depigmented area on the scalp that was also associated with histopathologic features suggestive of AA [13]. On revising the literature, no studies detailing the dermoscopic features of the hair in vitiligo lesions in different body areas could be found.

### Objectives

The objective of this study was to explore the dermoscopic features of the hair in vitiligo lesions in different body sites and their relation to disease duration.

### Methods

This study included 47 non segmental vitiligo patients of both sexes with more than one patch of vitiligo.

**Exclusion criteria for lesion choice:**

1. Lesions in areas anatomically known to have absent or sparse hair, eg palms, soles, mucous membranes, fingers and dorsum of the foot.
2. Scalp lesions, as it is difficult to evaluate vitiligo without shaving due to high hair density.
3. If all lesions in the same patient were of less than or more than two-year duration.
4. Segmental vitiligo.
5. Patients with a concomitant diagnosis of AA or with history of previously developing AA.

An informed consent was signed by each patient after the technical and scientific basis of the research project and the steps of the procedure were explained in details. The research was approved by the local Medical Ethics Committee (approval number: 0303878/14/03/2018).

Each patient was examined clinically and two vitiligo lesions (one old and one recent) were selected for examination; recent lesions were of a duration of less than two years and old lesions were of a duration of two or more years [14]. Lesions and surrounding control areas were photographed using a digital camera (Samsung ST66, 16 megapixels); photos were taken from a constant distance and under similar photographing conditions. The hair within the lesions was evaluated using the Medicam 1000 video-dermoscope (Fotofinder). Three shots were taken with the videodermoscope (20X magnification) from the vitiligo lesion and three shots were taken from perilesional normally pigmented skin (control) after Wood’s light examination was done to exclude the presence of subclinical vitiligo. The dermoscopic photos were evaluated by Trichoscale® Pro program (Fotofinder). The report of every photo included data about hair density, anagen and telogen hair rates, terminal and vellus hair rates and the mean hair shaft thickness. The means of the collected data from the reports of the three shots taken from every lesional and perilesional normally pigmented skin were determined. In addition, videodermoscopic photos of the studied lesions and perilesional control areas were evaluated for the presence of dermoscopic signs of alopecia areata such as black dots, tapering hair, broken hair, yellow dots, short vellus hair, circular (pigtail) hair, upright re-growing hair and Pohl-Pinkus constriction.

### Statistical Analysis

The collected data was analyzed using the statistical package for Social Science (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp.). Quantitative variables were tested for normality of distribution using the Kolmogorov-Smirnov test and were expressed as median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Paired nominal variables were compared using McNemar-Bowker test. Differences between paired continuous data (lesions and control areas) were tested using the Wilcoxon signed rank test. The strength of association between the two quantitative variables was assessed using Spearman method. A P value less than 0.05 was considered statistically significant.

### Results

The age of the patients ranged from 7 to 55 years (mean: 26.38 ± 14.5 years). Twenty-four males (51%) and 23 females (49%) were enrolled in the study. The mean duration of the
included recent vitiligo lesions (< 2 years) was 6.28 ± 2.37 months while the mean duration of the included old vitiligo lesions (≥ 2 years) was 46.8 ± 18.72 months.

Hair Changes in Recent Lesions
In recent vitiligo lesions, anagen hair rate, anagen to telogen ratio, terminal hair rate and terminal to vellus ratio were lower than those in the respective control areas, but the difference was not significant (P = 0.352, 0.783, 0.603 and 0.656, respectively). Furthermore, hair density, telogen hair rate, and vellus hair rate were higher in recent vitiligo lesions compared to control areas, and the difference was also not significant (P = 0.151, 0.352 and 0.603, respectively) (Table 1).

Hair Changes in Old Lesions
In old vitiligo lesions, hair density, terminal hair rate, terminal to vellus ratio and mean hair thickness were significantly lower (P < 0.001, 0.011, 0.029 and 0.031, respectively), whereas vellus hair rate was significantly higher (p=0.011) than in the perilesional control areas. No significant difference between old patches and their control areas regarding anagen and telogen hair rates and anagen to telogen ratio was detected (P = 0.195, 0.195 and 0.357, respectively) (Table 2). The decrease in hair density and thickness in old vitiligo lesions compared to their respective control sites is shown in Figure 1.

Dermoscopic Signs of the Hair in Vitiligo Lesions
In old lesions, the most commonly encountered sign was broken hair, which was seen in 51.1% of the patients, followed by pig tail hair in 31.9% of the patients. Meanwhile, tapering hair and Pohl-Pinkus constriction were the least commonly encountered signs, as each was detected in 8.5% of patients. In recent vitiligo patches, short vellus hair was detected in 31.9% of the patients followed by upright regrowing hair in 29.8% of the patients. The least commonly encountered sign was tapering hair that was detected in 4.3% of the patients. None of the recent vitiligo patches showed Pohl-Pinkus constriction. The presence of broken hair was significantly higher, whereas the presence of upright regrowing hair was significantly lower in old patches compared to recent patches (P <0.001 and 0.016, respectively) (Table 3). On comparing old vitiligo lesions to their respective controls, the frequency

### Table 1. Comparison between hair changes in recent vitiligo patches and their respective control patches.

<table>
<thead>
<tr>
<th></th>
<th>Recent patches (N = 47)</th>
<th>Control of recent patches (N = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair density (hair/cm²)</td>
<td>52.00 (23.20 – 81.90)</td>
<td>45.40 (17.70 – 96.30)</td>
<td>0.151</td>
</tr>
<tr>
<td>Anagen hair rate (%)</td>
<td>51.70 (33.10 – 65.30)</td>
<td>53.50 (37.50 – 66.70)</td>
<td>0.352</td>
</tr>
<tr>
<td>Telogen hair rate (%)</td>
<td>48.30 (34.70 – 66.90)</td>
<td>46.50 (33.30 – 62.50)</td>
<td>0.352</td>
</tr>
<tr>
<td>Anagen to telogen ratio</td>
<td>1.07 (0.49 – 1.88)</td>
<td>1.15 (0.60 – 2.0)</td>
<td>0.783</td>
</tr>
<tr>
<td>Terminal hair rate (%)</td>
<td>5.60 (0.0 – 19.40)</td>
<td>6.70 (0.0 – 18.0)</td>
<td>0.603</td>
</tr>
<tr>
<td>Vellus hair rate (%)</td>
<td>94.40 (80.60 – 100.0)</td>
<td>93.30 (82.0 – 100.0)</td>
<td>0.603</td>
</tr>
<tr>
<td>Terminal to vellus ratio</td>
<td>0.06 (0.0 – 0.24)</td>
<td>0.07 (0.0 – 0.22)</td>
<td>0.656</td>
</tr>
<tr>
<td>Mean thickness (mm)</td>
<td>0.028 (0.026 – 0.031)</td>
<td>0.028 (0.025 – 0.031)</td>
<td>0.414</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range); P value for Wilcoxon Signed Ranks Test.

### Table 2. Comparison between hair changes in old vitiligo patches and their respective control patches.

<table>
<thead>
<tr>
<th></th>
<th>Old patches (N = 47)</th>
<th>Control of old patches (N = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair density (hair/cm²)</td>
<td>33.20 (12.20 – 56.50)</td>
<td>78.60 (26.60 – 156.10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anagen hair rate (%)</td>
<td>48.10 (40.0 – 70.60)</td>
<td>61.60 (45.60 – 70.20)</td>
<td>0.195</td>
</tr>
<tr>
<td>Telogen hair rate (%)</td>
<td>51.90 (29.40 – 60.0)</td>
<td>38.40 (29.80 – 54.40)</td>
<td>0.195</td>
</tr>
<tr>
<td>Anagen to telogen ratio</td>
<td>0.92 (0.67 – 2.40)</td>
<td>1.60 (0.84 – 2.36)</td>
<td>0.357</td>
</tr>
<tr>
<td>Terminal hair rate (%)</td>
<td>10.30 (0.0 – 19.30)</td>
<td>17.10 (8.80 – 38.50)</td>
<td>0.011</td>
</tr>
<tr>
<td>Vellus hair rate (%)</td>
<td>89.70 (80.70 – 100.0)</td>
<td>82.90 (61.50 – 91.20)</td>
<td>0.011</td>
</tr>
<tr>
<td>Terminal to vellus ratio</td>
<td>0.11 (0.0 – 0.24)</td>
<td>0.21 (0.10 – 0.63)</td>
<td>0.029</td>
</tr>
<tr>
<td>Mean thickness (mm)</td>
<td>0.029 (0.025 – 0.031)</td>
<td>0.031 (0.029 – 0.035)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Data are expressed median (interquartile range); P value for Wilcoxon Signed Ranks Test.
Figure 1. Decreased hair density and thickness in old vitiligo lesions compared to their respective control sites (magnification x20). (A-C) Videodermoscopic photos of the hair changes in the old vitiligo lesions. (D-F) Video-dermoscopic photos of respective control sites. (A, B, D and E on the nape, C and F on the leg).

Table 3. Comparison between old and recent vitiligo patches regarding dermoscopic features of alopecia areata incognita.

<table>
<thead>
<tr>
<th></th>
<th>Old patches (N = 47)</th>
<th>Recent patches (N = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black dots, N (%)</td>
<td>6 (12.8%)</td>
<td>9 (19.1%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Tapering hair, N (%)</td>
<td>4 (8.5%)</td>
<td>2 (4.3%)</td>
<td>0.500</td>
</tr>
<tr>
<td>Broken hair, N (%)</td>
<td>24 (51.1%)</td>
<td>8 (17.0%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yellow dots, N (%)</td>
<td>8 (17%)</td>
<td>6 (12.8%)</td>
<td>0.500</td>
</tr>
<tr>
<td>Short vellus hair, N (%)</td>
<td>11 (23.4%)</td>
<td>15 (31.9%)</td>
<td>0.125</td>
</tr>
<tr>
<td>Circular (pig tail) hair, N (%)</td>
<td>15 (31.9%)</td>
<td>11 (23.4%)</td>
<td>0.125</td>
</tr>
<tr>
<td>Upright re-growing hair, N (%)</td>
<td>7 (14.9%)</td>
<td>14 (29.8%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Pohl-Pinkus constrictions, N (%)</td>
<td>4 (8.5%)</td>
<td>0 (0.0%)</td>
<td>0.125</td>
</tr>
</tbody>
</table>

P for McNemar-Bowker test
of broken hair, yellow dots and pig tail hair was significantly higher in the former (P < 0.001, 0.031, 0.004, respectively). Meanwhile, black dots and pig tail hair were significantly higher in recent vitiligo lesions than in control areas (P = 0.004 and 0.031, respectively).

Conclusions

In vitiligo, skin involvement usually precedes hair involvement. Nevertheless, lesions where leukotrichia developed prior to skin depigmentation have been reported, which was believed to result from preferential involvement of follicular melanocytes in such cases [15,16].

Several changes have been reported in association with vitiligo that include ocular, auditory and even nail changes [2,3,17]. Apart from the color change, little is known about the changes that could occur in the hair within vitiligo lesions. Reports of AA and vitiligo existing in the same individual are present [18], and several reports of co-localization of vitiligo and AA exist in the literature, most of which describe complete loss of hair in the depigmented patch with few white peripheral hairs. On histopathologic examination of the involved areas, features of vitiligo and AA were detected. Most of these cases were reported in young age and were mostly located on the scalp [9-12,19]. Walker et al. reported slight reduction in hair density within a localized area of poliosis on the scalp with depigmentation of the underlying skin in a male patient. Skin biopsies revealed features of both vitiligo and AA [13]. However, none of those reports studied the dermoscopic hair changes within the vitiligo lesions.

In the present study, the anagen-to-telogen and the terminal-to-vellus ratios were lower in both old and recent areas compared to their respective controls but the difference was significant only in the terminal-to-vellus ratio in old lesions. Furthermore, both old and recent vitiligo lesions exhibited dermoscopic findings such as yellow dots, broken hair, short vellus hair, upright regrowing hair and circular hair. These detected changes exhibit a certain degree of similarity to hair changes previously reported in alopecia areata incognita (AAI), which is characterized by the absence of a smooth bald surface, increased telogen hairs [20], yellow dots, upright regrowing hairs [21], black dots, short vellus hair, broken hair, and tapered hair [21-24]. AAI usually shows increased proportion of telogen and vellus hairs [25], resulting in decreased terminal-to-vellus and anagen-to-telogen ratios in patients compared to normal subjects [21,26,27].

The similarities between hair changes detected in the present study and those reported in AAI could be explained by the proposed immunologic link between vitiligo and AA; as both diseases are considered cell mediated autoimmune diseases in which disease induction, at least in part, has been attributed to an increase in cytotoxic CD8+NKG2D+ T cells together with over expression of interferon gamma (IFN-γ), with the involvement of the JAK-STAT signaling pathway [8]. In addition, it has been shown that the immunologic attack of CD8+ T-cells on follicular melanocytes can in some instances result in both depigmentation and hair loss [28]. Clinically, the fact that non-pigmented hairs are usually spared in alopecia areata, and regrowing hairs are initially depigmented, further links alopecia areata to melanocytes [29].

It has been proposed that autoreactive T-cells against melanogenesis-associated proteins are responsible for sparing white hairs in AA and for the transient regrowth of hypo-pigmented hairs. However, there is always an exception to the rule; as in some patients non-pigmented hairs were lost as well, and in others re-growing white hairs persisted. Furthermore, some patients never experience hair regrowth following the initial attack. These different outcomes suggest the existence of various antigens and various pathways involved that ultimately determine the fate of the immunologic attack on the hair follicle [30].

Unlike the findings of Walker et al. [13], hairs within the examined lesions were not exclusively depigmented, and in addition to decreased density, they also exhibited decreased thickness and decreased terminal to vellus ratio owing to an increase in vellus hair rate and a decrease in terminal hair rate. These changes, however, were only detected in old lesions. Unfortunately, the software program used in the current study digitally documents the essential hair parameters of all hairs in the lesion regardless of their color; accordingly, determining if the detected changes were influenced by hair color was not possible.

The role of disease duration in vitiligo has been previously studied and the presence of melanocytes in the hair follicles in vitiligo lesions was reported to be inversely correlated with disease duration [31]. In addition, shorter disease durations were associated with better treatment response to phototherapy [32]. In the present study, old and recent vitiligo lesions were compared with their respective controls. All significant videodermoscopic hair changes were exclusively seen in old vitiligo lesions.

These findings further point to the possible influence of disease duration in vitiligo. It seems that the insult to vitiligo skin is done through two waves with two different onsets, a first wave affecting epidermal melanocytes resulting in leukoderma, followed by a second wave affecting the hair leading to subtle hair changes, and if the insult of this wave is severe enough, leukotrichia can occur. The possibility that these hair changes could be the forerunners of leukotrichia remains to be determined.

To conclude, this study demonstrated that the hair involvement within vitiligo patches is not merely a color
change, and that these changes may serve as an objective clue to the duration of vitiligo lesions. The resemblance between the detected changes and some of the known features of AAI adds a new item to the list of similarities between AA and vitiligo. Accordingly, further research combining dermoscopic examination with histopathologic evaluation of the hair changes in vitiligo lesions and studying the relation of these changes to disease activity and severity is recommended.

References


Evaluating the Perception of Mycosis Fungoides Patients About Their Disease Before and After Educating Them

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**Key words:** Mycosis Fungoides, illness perception, Illness Perception Questionnaire-Revised, cutaneous T-cell lymphomas

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**Authorship:** All authors have contributed significantly to this publication.

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**ABSTRACT**

**Introduction:** Patient-held beliefs are important for disease management and few studies have evaluated illness perception of Mycosis Fungoides (MF) patients.

**Objectives:** Here, we aimed to determine the effect of educating MF patients on their perception of their disease.

**Methods:** Patients with diagnosed MF were asked to fill the Illness Perception Questionnaire-Revised (IPQ-R) once before education and once 3 months later.

**Results:** Fifty-five patients, 41 men and 14 women, with a mean age of 45.5 ± 13.9 years were enrolled. Regarding the main etiologic factor, most patients cited anxiety (91%). After education, the most significant changed belief on disease etiology was immune system dysfunction and the change was twenty-six percent which was observed more in patients with higher educational levels, shorter disease duration, and lower MF stages. Regarding the most prevalent clinical manifestations, most patients mentioned erythema (86%). After education, the greatest change in symptom perception was related to lymphadenopathy (32%) which was significantly associated with less disease duration and those treated with phototherapy. Before education, the mean perception score about the disease chronicity was 23.67 ± 3.549 that increased to 27.71 ± 1.66 (P < 0.001). This change was more observed in men (P = 0.03), those with less disease duration, and those treated with phototherapy.
Introduction

Mycosis Fungoides (MF) is the most common type of cutaneous T-cell lymphomas (CTCL). The annual incidence of MF is estimated at approximately 6:1,000,000 [1-3]. The common age of onset is 55-60 years, and the prevalence of the disease in men is reported to be 2 times higher than in women [2-4].

The most common clinical manifestations of MF are slowly progressive patches and plaques on the trunk that might be scaly or pruritic [5,6].

Due to the long course of the disease, patients with MF will experience annoying symptoms such as pain and itch for a considerable period of time, and their skin lesions may lead to social anxiety, embarrassment, and isolation [7]. Also, currently available treatments do not cause long-lasting remis-

The concept of illness perception is based on Leventhal self-regulatory model and deals with the relationship between the nature of the disease, the patient concern about the disease, coping processes, and health outcomes [9,10]. Patient-held beliefs are very important for the clinical management of their disease. Also, it has been proved that acquiring more knowledge about the disease is associated with a better understanding of the illness and more personal and treatment control [11].

In previous studies on MF, patients illness perception was assessed in a one-time examination or in two-time assessments without any educational intervention regarding the disease between the two evaluations. Hence, the data in this area is lacking.

Objectives

Since MF patient interpretation and perception can affect different aspects of their lives, this study aimed to determine the effect of educating MF patients on their perception of their disease.

Methods

Participants, Questionnaire, and Data Collection

An analytical, cross-sectional study was conducted in Razi dermatology hospital, Tehran, Iran from March 2020 to July 2020. The study was approved by the ethical committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.266). Information about the study was given to all participants and each participant signed a form of consent for taking part in our study.

Sixty patients with MF diagnosed based on both clinical and histopathological studies aged between 19 and 74 years were enrolled in the study.

A checklist including demographic and clinical characteristics of participants was filled out for each patient. Afterward, the patients were asked to fill the Illness Perception Questionnaire-Revised (IPQ-R) once before educating them on their disease characteristics and once 3 months after the education. The given education included patient-oriented information about MF etiology, prevalence, clinical manifestations, diagnosis, treatment, and the prognosis given in the format of an educational catalog. The educational material was first explained to all patients by a dermatologist and then given to them for further reading. Of 60 participants who completed the IPQ-R questionnaire in the first assessment, 5 did not complete the questionnaire in the second round.

The IPQ-R had been previously translated to the Persian language and its validity and reliability were confirmed [12]. The IPQ-R evaluates patients’ perspectives across seven subscales: timeline acute/chronic, timeline-cyclical, consequences, personal control, treatment control, illness coherence, and emotional representations. Moreover, a checklist of clinical symptoms was shown to patients and they were asked to choose the most important factors causing their disease from a checklist of possible etiologic factors (supplementary file 1).

Data Analysis

Statistical analysis was performed by using IBM SPSS Statistics 26. Frequency and percentage were reported for qualitative variables, and mean and standard deviation for quantitative variables. To compare the mean scores between discrete independent variables, independent T-test and one-way Anova test was used. Also, the Pearson correlation coefficient was used to evaluate the correlation between continuous variables. A P of less than 0.05 was considered as significant.

Results

Sociodemographic Characteristics

A total of fifty-five patients, 41 (74.5%) men and 14 (25.5%) women, with the mean age of 45.5 ± 13.9 years (range 19-74) were enrolled in the study. The demographic data are

Conclusions:

Generally, MF patients hold favorable perspectives about their disease and educating them positively improves their illness perception. Patients with higher educational levels and lower stages of the disease showed more significant changes in various aspects of illness perception. Hence, early education is recommended in patients with lower educational levels.
shown in Table 1. Considering the stage of the disease, the most prevalent stages among 55 patients were stage IA in 18 (32.7%) and stage IB in 14 (25.5%), respectively (Table 1).

### Beliefs About the Cause of the Disease

Before educating the patients, the most common etiologic factors associated with their disease based on patients’ beliefs were stress and anxiety (91%), familial worries and problems (82%), and emotional states (76%). While after educating the patients, the most prevalent etiologic factors were stress and anxiety (94%), familial worries (83%), and immune system dysfunction (73%). After educating the patients, the most significant change in the mean score of perception about the disease etiology was related to immune system dysfunction (26%), smoking and drug abuse (20%), and hereditary factors. This change was reported more in patients with higher educational levels, lower stages of the disease, and shorter illness duration.

### Beliefs About Illness Coherence

Before training, the achieved score about patients’ illness coherence was 13.82 ± 3.65 and after the training, this score was 17.80 ± 2.81 (range 5-25). This proves that most patients had an acceptable knowledge about their disease and after the training, their knowledge improved (P < 0.001). After educating the patients, the educational level had a positive relationship with illness coherence (P < 0.001) and with the changes in patients’ beliefs about illness coherence (P = 0.019). Also, there was a negative relationship between patients’ age and their beliefs about illness coherence (P = 0.004).

### Beliefs About the Symptoms

Before educating the patients, the most common reported symptoms were erythema (86%), pruritus (75%), and scaling (68%). In the second assessment, the first three common symptoms were again erythema (100%), pruritus (92%), and scaling (84%), but they were different from those in

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<p>| Table 1. Sociodemographic characteristics of the patients. |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean ± SD</strong></td>
<td>45.5 ± 13.9</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>41 (74.5%)</td>
</tr>
<tr>
<td>female</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>Marital status, N (%)</td>
<td></td>
</tr>
<tr>
<td>single</td>
<td>16 (29.1%)</td>
</tr>
<tr>
<td>married</td>
<td>39 (70.9%)</td>
</tr>
<tr>
<td>Education level, N (%)</td>
<td></td>
</tr>
<tr>
<td>under high school diploma</td>
<td>20 (36.4%)</td>
</tr>
<tr>
<td>high school diploma and associate degree</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>bachelor and master degree</td>
<td>17 (30.9%)</td>
</tr>
<tr>
<td>doctorate and more</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Duration of the disease, N (%)</td>
<td></td>
</tr>
<tr>
<td>less than 2 years</td>
<td>20 (36.4%)</td>
</tr>
<tr>
<td>2-4 years</td>
<td>23 (41.81%)</td>
</tr>
<tr>
<td>4-6 years</td>
<td>6 (10.90%)</td>
</tr>
<tr>
<td>6-8 years</td>
<td>4 (7.27%)</td>
</tr>
<tr>
<td>8-10 years</td>
<td>2 (3.63%)</td>
</tr>
<tr>
<td>Stage of the disease, N (%)</td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>Stage IB</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>7 (12.7%)</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>9 (16.4%)</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>3 (5.5%)</td>
</tr>
<tr>
<td>Skin lesions, N (%)</td>
<td></td>
</tr>
<tr>
<td>patch</td>
<td>23 (41.8%)</td>
</tr>
<tr>
<td>plaque</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>cutaneous tumor</td>
<td>10 (18.2%)</td>
</tr>
<tr>
<td>generalized erythema</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Palpable lymph nodes, N (%)</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>37 (67.3%)</td>
</tr>
<tr>
<td>yes</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>Type of treatment, N (%)</td>
<td></td>
</tr>
<tr>
<td>phototherapy</td>
<td>39 (70.9%)</td>
</tr>
<tr>
<td>phototherapy with additional treatment</td>
<td>16 (29.1%)</td>
</tr>
</tbody>
</table>
about the negative consequences of their illness and this attitude increased after the training (P = 0.005). After the training, the stage of the disease had a positive relationship with beliefs about consequences (P > 0.001).

Beliefs About Cure and Control
The achieved score before and after the training was 20.69 ± 3.82 and 23.71 ± 2.85, respectively (P < 0.001) indicating that most of the patients were aware of their role in controlling their disease and this increased significantly after the training. Also, comparing the scores of their beliefs about treatment control before (18.60 ± 3.010) and after (22.45 ± 1.74) the training showed that most patients believed that treatment has an acceptable role in controlling the disease and improving the clinical symptoms (P < 0.001). Moreover, the educational level had a positive relationship with the changes in beliefs about treatment control (P = 0.011).

Beliefs About Emotional Representation
Before informing the patients, the mean perception score about the disease chronicity was 23.67 ± 3.549; after educating the patients, this score was 27.71 ± 1.66 (range 6-30). The given scores show that most patients accepted that their disease is a chronic situation and this attitude increased significantly after training (P < 0.001). Regarding the disease timeline-cyclical, before and after training, the scores were 13.00 ± 2.40 (range 4-20) and 16.31 ± 1.78 (range 4-20), respectively. This shows that most patients consider their illness as a recurrent situation and this belief increased significantly after the training (P < 0.001). Beliefs about the disease chronicity changed significantly after the training in both genders and it was more prominent in men (P = 0.03). After educating the patients, as the educational level increased, the awareness about the disease chronicity increased (P < 0.001). After the training, the stage of the disease had a positive relationship with beliefs about the chronicity of the disease (P < 0.001).

Conclusions
MF is the most common type of CTCL and can influence various aspects of patients’ lives. The results of our study show that after informing the patients about their illness, the greatest change in terms of symptom perception was related to lymphadenopathy (32%), pruritus (17%), and scaling (16%). The change in patients’ beliefs was more pronounced in patients with shorter disease duration, patients with patches and plaques type lesions, and those receiving phototherapy.

### Table 2. Perception modalities before and after educating the patients.

<table>
<thead>
<tr>
<th>Perception Modalities</th>
<th>Mean</th>
<th>Number</th>
<th>Standard Deviation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timeline-Acute/Chron. 1</td>
<td>23.67</td>
<td>55</td>
<td>3.549</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Timeline-Acute/Chron. 2</td>
<td>27.71</td>
<td>55</td>
<td>1.663</td>
<td>0.005</td>
</tr>
<tr>
<td>Consequences 1</td>
<td>18.53</td>
<td>55</td>
<td>3.681</td>
<td>0.005</td>
</tr>
<tr>
<td>Consequences 2</td>
<td>19.55</td>
<td>55</td>
<td>3.366</td>
<td></td>
</tr>
<tr>
<td>Personal control 1</td>
<td>20.69</td>
<td>55</td>
<td>3.829</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Personal control 2</td>
<td>23.71</td>
<td>55</td>
<td>2.859</td>
<td></td>
</tr>
<tr>
<td>Treatment control 1</td>
<td>18.60</td>
<td>55</td>
<td>3.010</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Treatment control 2</td>
<td>22.45</td>
<td>55</td>
<td>1.741</td>
<td></td>
</tr>
<tr>
<td>Illness coherence 1</td>
<td>13.82</td>
<td>55</td>
<td>3.657</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Illness coherence 2</td>
<td>17.80</td>
<td>55</td>
<td>2.811</td>
<td></td>
</tr>
<tr>
<td>Timeline-cyclic 1</td>
<td>13.00</td>
<td>55</td>
<td>2.404</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Timeline-cyclic 2</td>
<td>16.31</td>
<td>55</td>
<td>1.783</td>
<td></td>
</tr>
<tr>
<td>Emotional representation 1</td>
<td>22.35</td>
<td>55</td>
<td>5.372</td>
<td>0.004</td>
</tr>
<tr>
<td>Emotional representation 2</td>
<td>24.00</td>
<td>55</td>
<td>3.031</td>
<td></td>
</tr>
</tbody>
</table>

1= BEFORE; 2= AFTER.
indicate that MF patients have an acceptable understanding of their disease, its causing factors, and clinical manifestations associated with their disease which significantly increases after training them.

The fact that patients have an acceptable perception of their illness has been confirmed in previous studies on various dermatologic diseases including vitiligo and skin cancers and is consistent with our study [13-15]. A study by Topal et al on 100 vitiligo patients using IPQ suggested that patients had good knowledge about their disease and were highly aware of the etiologic factors [14]. Despite the low prevalence of MF, the patients in our study had a good knowledge about their disease which significantly increased after educating them. The opposite results were observed in a study done by Eder et al that believed patients with CTCL have a poor understanding of their disease. This poor knowledge was attributed to the low prevalence of the disease and the unknown cause of CTCL [8].

Our study showed that educating MF patients cause significant changes in beliefs about different factors such as the etiologic factors, clinical manifestations, disease chronicity and recurrence, emotional impacts, illness consequences, personal control, and treatment control. These changes indicate that educating MF patients help them to have a better knowledge about their illness. Generally, changes in patients perception about the clinical manifestations, consequences, and emotional representations were more notable than other variables after the education.

Regarding the main etiologic factor, the results of our study showed that most patients with MF cited stress and anxiety as the main causing factor for their illness. The same results were also found in Firooz et al study which assessed 80 vitiligo patients using IPQ and observed that a total of 62.5% of patients believed that stress was a major factor in causing their disease [13]. After the education, the greatest change in the knowledge of patients in etiology was observed in patients with higher educational levels, shorter disease duration, and lower stages of MF. This indicates that educating MF patients as early as possible may have a better influence on patients perception of their disease. It is worth mentioning that after the education, patients with lower educational levels did not show significant changes regarding the etiologic factors which highlight the point that more efforts should be made in educating these groups of patients and different means of education rather than a single brochure should be considered for them.

In terms of clinical manifestations, most of our patients mentioned erythema, pruritus, and scaling as the most prevalent clinical manifestations. After instructing the patients about their illness, the greatest change in terms of symptom perception was related to lymphadenopathy meaning that lymphadenopathy might not be noticed by patients if the physicians do not educate patients about it. After educating them, the greatest change in the amount of knowledge about the MF clinical signs was observed in those with less disease duration, those who manifested patches or plaques and those who were being treated with phototherapy. This finding can be suggestive of the fact that educating those who are only treated with medications does not result in a desirable change in their illness perceptions in comparison to therapies such as phototherapy that requires more visits by the physicians.

Our study shows that MF patients have an acceptable knowledge about the chronic and recurrent nature of their disease that significantly increases after training especially in men, those with less disease duration, and those who were only treated with phototherapy. As seen in Fortune et al that investigated 162 patients with psoriasis and observed that a vast majority of patients believed their disease was more likely to be chronic or recurrent, while only a short number of them considered their condition to be temporary [16].

Regarding the beliefs about the disease negative consequences, after the education, patients had a better understanding of their diseases’ negative consequences, especially in those with higher stages of MF.

MF has a severe negative emotional impact on patients that significantly increases after educating them. Although a negative perception about the consequences of illness is not the equivalent of having a psychiatric disorder, it may increase the likelihood of developing the disorder [16]. The greatest change regarding the negative emotional feelings toward the disease was observed in those with less disease duration and those who had lower stages of MF. Since the greatest changes in patients illness perception were observed among patients with less disease duration and lower stages of the disease, it is important to educate patients in the early stages of their illness.

Most of our patients believed that they have an important role in controlling their illness that significantly improved after educating them. The greatest change in this belief was observed in those with higher educational levels. Notably, in Eder et al study, it was observed that patients had limited belief in personal control, but a strong belief in treatment control which was attributed to their sample consisting of patients with long disease duration [8]. In general, MF patients hold favorable perspectives about their disease and educating them positively improves their views about their illness. Also, patients with higher educational levels and lower stages of the disease showed more significant changes in various aspects of illness perception. Hence, early education is recommended in patients with lower educational levels. More research on increasing MF patients understanding of their illness should be done, since correcting patients misconceptions is associated with increased follow-up and improved treatment outcomes.
References


The Accuracy of Clinical Diagnosis in 2135 Lesions on the Face. A Retrospective Analysis of Histopathological Records

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Key words: dermatopathology, cancer, standardized skin surface biopsy, face, inflammatory diseases


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ABSTRACT

Introduction: Biopsy of facial skin lesions is an important supplement to dermatological diagnostics, especially in doubtful cases or suspected of being malignant.

Objectives: The aim of the retrospective study of 2135 histopathological records of lesions on the face was to: establish the most common indications for a skin biopsy in patients with facial lesions, establish the frequency of histopathological diagnoses, evaluate how often clinically suspected inflammatory lesions are identified as tumors in histopathology, evaluate the accuracy of clinical diagnoses of the most common skin tumors and dermatoses.

Methods: It was a retrospective study. Histopathological records from the lesions on the face from years 2010-2017 were analyzed.

Results: The mean age of patients was 69.3 [7-98]. Fifty-eight percent of the patients were women. Among 2135 clinical diagnoses skin tumors were suspected in 1905 cases. Among 2169 obtained histopathological results (34 biopsies showed 2 diseases), we identified skin tumors in 1940 cases, with 1388 confirmed as malignant. The clinical diagnosis of a specific benign or malignant skin tumor was accurate in 1013/1634 subjects, in comparison to inflammatory lesions, which were correct in 67/148 cases, (P = 0.0001). Among all preliminary inflammatory diagnoses, 33/204 lesions were identified as skin tumors in histopathology.
Introduction

Face is one of the special locations in dermatology with skin lesions easily visible having a negative impact on self-esteem and decreasing the quality of life. Many dermatoses on the face are easily diagnosed based on clinical examination and dermoscopy, and no skin biopsy is needed. Dermoscopic criteria of skin tumors on the face are well established and used in everyday clinical practice [1]. Also dermoscopic patterns of common facial inflammatory lesions were shown by Lallas et al [2].

However, in doubtful cases, when malignancy is suspected, a histopathological examination is mandatory, despite the fact, that skin biopsy may result in scar formation.

Objectives

The aim of the study was to analyze the histopathological records from lesions on the face, to define the most common indications for a skin biopsy, to establish the order of the common histopathological diagnoses, to evaluate how often skin biopsies suspected as inflammatory lesions turn out to be skin tumors, to evaluate the accuracy (the same clinical and histopathological diagnoses) of the most common skin tumors and dermatosis on the face.

Methods

It was a retrospective study performed at the Department of Dermatology, Medical University of Warsaw, Poland. Histopathological records from the lesions on the face from years 2010-2017 were analyzed. Patients for skin biopsies (punch, shave or excisional) were referred from our department as well as from many outpatients clinics in Warsaw area. The patients presented with skin phototypes I-III. The mean age of patients was 69.3 (range 7-98 years of age), and 58.28% of patients were women. Biopsies taken from the scalp and mucous membranes were excluded. A total number of 89 cases were nondiagnostic and were excluded from the study. In total 2135 biopsy records were evaluated, 750 from cheeks with zygomatic area, 718 from noses, 434 from foreheads, 110 from ears, 71 from lips and 52 from chins. Because in 34 cases 2 final diagnoses were established a total number of 2169 of final diagnoses were analyzed.

Statistical Analysis

The results were computed with Statistica 13.1 software (StatSoft Incorporated) licensed to the Medical University of Warsaw. Chi 2 test was used for assessing binary variables. A P value below 0.05 was considered statistically significant.

Results

Among 2135 clinical diagnoses, the skin tumors were suspected in 1905 (89.23%) cases, and in 1609 (75.36%) cases malignant skin tumor or precancerous lesion were considered.

Table 1. The most common clinical diagnoses (≥ 3 cases) among 2135 skin biopsies. In some cases, more than one clinical diagnosis was given

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total number of cases</th>
<th>%</th>
<th>CHEEK</th>
<th>CHIN</th>
<th>EAR</th>
<th>FOREHEAD</th>
<th>LIPS</th>
<th>NOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell carcinoma</td>
<td>984</td>
<td>46.09%</td>
<td>313</td>
<td>18</td>
<td>51</td>
<td>196</td>
<td>27</td>
<td>379</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>424</td>
<td>19.86%</td>
<td>149</td>
<td>5</td>
<td>14</td>
<td>102</td>
<td>4</td>
<td>150</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>108</td>
<td>5.06%</td>
<td>40</td>
<td>0</td>
<td>6</td>
<td>30</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Fibroma</td>
<td>105</td>
<td>4.92%</td>
<td>49</td>
<td>5</td>
<td>3</td>
<td>11</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>Squamous cell carcinoma, keratoacanthoma</td>
<td>96</td>
<td>4.5%</td>
<td>22</td>
<td>4</td>
<td>17</td>
<td>12</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>88</td>
<td>4.12%</td>
<td>58</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>
Table 2. The most common histopathological diagnoses (≥3 cases) among 2169 skin biopsies. The number of the correct diagnoses in the most common skin lesions † clinical diagnosis was confirmed by histopathological examination; SCC, squamous cell carcinoma

<table>
<thead>
<tr>
<th>Clinical diagnoses</th>
<th>Total number of cases</th>
<th>%</th>
<th>CHEEK</th>
<th>CHIN</th>
<th>EAR</th>
<th>FOREHEAD</th>
<th>LIPS</th>
<th>NOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous horn</td>
<td>52</td>
<td>2.44%</td>
<td>23</td>
<td>3</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Melanocytic nevus, blue nevus</td>
<td>38</td>
<td>1.78%</td>
<td>10</td>
<td>7</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>37</td>
<td>1.73%</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Skin tumor</td>
<td>32</td>
<td>1.50%</td>
<td>9</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>23</td>
<td>1.08%</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Verruca vulgaris</td>
<td>23</td>
<td>1.08%</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Solar lentigo</td>
<td>14</td>
<td>0.66%</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Facial granuloma</td>
<td>13</td>
<td>0.61%</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Rosacea</td>
<td>10</td>
<td>0.47%</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Eczema</td>
<td>8</td>
<td>0.37%</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>8</td>
<td>0.37%</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7</td>
<td>0.33%</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Granulomatous cheilitis</td>
<td>6</td>
<td>0.28%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma in situ. Bowen type</td>
<td>6</td>
<td>0.28%</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Annular granuloma</td>
<td>6</td>
<td>0.28%</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sebaceous hyperplasia</td>
<td>5</td>
<td>0.23%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cyst</td>
<td>4</td>
<td>0.19%</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>4</td>
<td>0.19%</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytoma</td>
<td>4</td>
<td>0.19%</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis (superficial dermal inflammation)</td>
<td>3</td>
<td>0.14%</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Morphea</td>
<td>3</td>
<td>0.14%</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical diagnoses</th>
<th>Number of the correct diagnoses (%)</th>
<th>Number of the correct diagnoses in total (%)</th>
<th>Number of cases with a skin tumor in histopathological diagnosis (%)</th>
<th>Number of cases with a skin tumor in histopathological diagnosis in total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN TUMORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>629/984 (63.92)</td>
<td>1013/1634 (61.99)</td>
<td>342/355 (96.33)</td>
<td>583/621 (93.88)</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>282/424 (66.51)</td>
<td></td>
<td>124/142 (85.21)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma in situ, Bowen type</td>
<td>2/6 (33.33)</td>
<td></td>
<td>0/0 (100)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>29/74 (39.19)</td>
<td></td>
<td>42/45 (93.33)</td>
<td></td>
</tr>
<tr>
<td>Melanocytic nevus</td>
<td>22/38 (57.89)</td>
<td></td>
<td>16/16 (100)</td>
<td></td>
</tr>
<tr>
<td>Sebaceous keratosis</td>
<td>49/108 (45.37)</td>
<td></td>
<td>58/59 (98.3)</td>
<td></td>
</tr>
<tr>
<td>INFLAMMATORY DERMATOSES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial granuloma</td>
<td>6/13 (46.15)</td>
<td>67/148 (45.27)</td>
<td>27/ (28.57)</td>
<td>19/81 (23.46)</td>
</tr>
<tr>
<td>Lupus erythematosus</td>
<td>49/88 (55.68)</td>
<td></td>
<td>12/39 (30.77)</td>
<td></td>
</tr>
<tr>
<td>Rosacea</td>
<td>5/10 (50.00)</td>
<td></td>
<td>1/5 (20)</td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>7/37 (18.92)</td>
<td></td>
<td>4/30 (13.33)</td>
<td></td>
</tr>
</tbody>
</table>
The most common clinical diagnosis was basal cell carcinoma (BCC), followed by actinic keratosis, seborrheic keratosis, fibroma, and cutaneous lupus erythematosus (Table 1).

Table 2 presents the most common clinical neoplasm and inflammatory diagnoses with the percentages of correct cases confirmed by histopathological examination. Clinical diagnoses of skin tumors were accurate in 1013/1634 (61.99%) cases, in comparison to inflammatory lesions, which were correct in 67/148 (45.27%) cases (P = 0.0001). Among 621 inaccurate clinical diagnoses of the most common skin tumors, 583 cases turned out to be other skin neoplasms (93.88%), and among 81 inaccurate clinical diagnoses of the most common inflammatory dermatoses 19 turned out to be skin neoplasms (23.46%)(P < 0.0001). Among all preliminary inflammatory diagnoses, 33/204 (16.17%) cases turned out to be skin malignancies, such as basal and squamous cell carcinomas.

Among 2169 histopathological diagnoses, skin tumors were diagnosed in 1940 (89.44%) cases, and malignant skin tumors were diagnosed in 1388 (63.99%) cases. The most common final diagnosis was basal cell carcinoma, followed by actinic keratosis, squamous cell carcinoma, fibroma, seborrheic keratosis, and cutaneous lupus erythematosus (Table 3).

Majority of basal cell carcinomas were present on the nose (306 cases from 737; 41.5%), followed by cheeks (200; 27.13%). The most common locations of actinic keratosis constituted cheeks (171 out of 447; 38.2%) and nose (161; 36%), whilst squamous cell carcinomas were distributed on the cheeks (49 out of 146; 33.6%), nose (41; 28%) and forehead (23; 15.8%) (Table 3).

The most common diagnosed inflammatory dermatoses included cutaneous lupus erythematosus on the first place, followed by rosacea, demodicosis, facial granuloma, and sarcoidosis. Among patients older than 65 years, 74.83% (1124/1502) of cases were malignant skin tumors in comparison to incidence of 39.58% (264/667) among patients aged ≤ 65 years (P < 0.00001).

As far as regions of the face are concerned, no statistical difference between numbers of correct diagnoses on the ear, nose, lips, and other regions on the face (cheeks, chin, forehead) was found (Table 4).

Conclusions

Face, which is constantly exposed to solar radiation is a common location for skin tumors. According to study of Ferreira et al on topographic distribution of basal cell carcinomas head and neck area was the most frequent location of the tumor (75.55%), followed by trunk (10.5%) [3]. In another study, over 60% of nonmelanoma skin tumors presented in the head area [4].

In our study, as suspected, the most common clinical and histopathological diagnosis was a tumor: basal and squamous cell carcinoma, actinic keratosis, seborrheic keratosis, and fibroma. The most common distributions of squamous cell carcinoma were the cheeks, nose and forehead, and for basal cell carcinoma were the nose and cheeks. The results were in line with the study of Kato et al [5]. It was shown in a group of 106 Japanese patients, that the cheek (54.2%) and forehead (25.5%) were the most common facial distribution of squamous cell carcinoma [5].

BCC has correctly resulted as the most frequent skin lesion on the face. Among the common skin lesions, the most incorrect diagnoses occurred in the case of squamous cell carcinoma (only 33-39% of cases were correctly diagnosed). Squamous cell carcinoma was misdiagnosed with (in order of the most common): BCC, actinic keratosis. Another clinically misdiagnosed pairs of lesions are: for BCC - actinic keratosis, squamous cell carcinoma, seborrheic keratosis, epidermal nevus, for actinic keratosis - BCC, squamous cell carcinoma, seborrheic keratosis, morbus Bowen, papilloma, for seborrheic keratosis - papilloma, actinic keratosis, BCC, verruca vulgaris and for fibroma - verruca vulgaris, seborrheic keratosis, inverted follicular keratosis, cutaneous horn.

What is interesting, the diagnosis of a skin tumor was correct in only 61.99% of cases. This means, that in many cases of a clinically suspicious lesion the histopathological diagnosis was a benign tumor. The results showed that approach with taking a diagnostic biopsy before performing surgical procedure is reasonable and the result influences the need and extent of surgery. In case of benign diagnosis, the remnants of the lesion can be left and no surgical procedure is required.

Among inflammatory dermatoses (10.56% of cases), the most common were in order cutaneous lupus erythematosus, rosacea, demodicosis, facial granuloma, and sarcoidosis. In the study only 45.27% of clinical diagnosis of inflammatory lesions were consistent with histopathological results. Among cases with suspicion of inflammatory dermatoses skin tumors were diagnosed. These results showed that in doubtful inflammatory lesions on the face the biopsy is recommended for two reasons. First of all, to exclude a malignant tumor. The second reason is to establish a final diagnosis. It should be underlined, that among inflammatory dermatoses such as cutaneous lupus erythematosus and sarcoidosis, systemic involvement can occur, and patients with such diseases need additional laboratory and imaging tests, therefore the correct diagnosis has special importance and requires medical follow-up.

The study has some limitations. It was a single-centre study. Another restriction of our study is the fact that some cases of skin tumors are not biopsied due to clear clinical and dermoscopic aspects. It includes all cases where these
Table 3. The number of the correct diagnoses in the most common skin lesions. The most common histopathological diagnoses (> 10 cases) among 2169 skin biopsies.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Total number of cases</th>
<th>%</th>
<th>CHEEK</th>
<th>CHIN</th>
<th>EAR</th>
<th>FOREHEAD</th>
<th>LIPS</th>
<th>NOSE</th>
<th>Age &lt;=65a</th>
<th>Age &gt;65a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin neoplasms in total</td>
<td>1940/2169</td>
<td>89.44</td>
<td>664/769</td>
<td>43/56</td>
<td>99/105</td>
<td>388/443</td>
<td>58/71</td>
<td>688/725</td>
<td>515/667 (77.21%)</td>
<td>1425/1502 (94.87%)</td>
</tr>
<tr>
<td>Malignant skin tumors in total</td>
<td>1388/2169</td>
<td>63.99</td>
<td>450/769</td>
<td>21/56</td>
<td>83/105</td>
<td>273/443</td>
<td>40/71</td>
<td>521/725</td>
<td>264/667 (39.58%)</td>
<td>1124/1502 (74.83%)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>737</td>
<td>33.98</td>
<td>200</td>
<td>18</td>
<td>40</td>
<td>151</td>
<td>22</td>
<td>306</td>
<td>160</td>
<td>577</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>447</td>
<td>20.61</td>
<td>171</td>
<td>0</td>
<td>14</td>
<td>92</td>
<td>9</td>
<td>161</td>
<td>77</td>
<td>370</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>146</td>
<td>6.73</td>
<td>49</td>
<td>2</td>
<td>22</td>
<td>23</td>
<td>9</td>
<td>41</td>
<td>22</td>
<td>124</td>
</tr>
<tr>
<td>Fibroma</td>
<td>125</td>
<td>5.76</td>
<td>49</td>
<td>5</td>
<td>3</td>
<td>32</td>
<td>4</td>
<td>32</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>108</td>
<td>4.98</td>
<td>45</td>
<td>0</td>
<td>5</td>
<td>39</td>
<td>0</td>
<td>19</td>
<td>35</td>
<td>73</td>
</tr>
<tr>
<td>Cutaneous lupus erythematosus</td>
<td>57</td>
<td>2.63</td>
<td>37</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>12</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Melanocytic nevus</td>
<td>56</td>
<td>2.58</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>20</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Squamous cell carcinoma in situ, Bowen type</td>
<td>46</td>
<td>2.12</td>
<td>24</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>12</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>Rosacea</td>
<td>37</td>
<td>1.71</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>6</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Inverted follicular keratosis</td>
<td>35</td>
<td>1.61</td>
<td>27</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>29</td>
<td>1.34</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Verruca vulgaris</td>
<td>27</td>
<td>1.24</td>
<td>10</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Cutaneous horn</td>
<td>26</td>
<td>1.20</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Demodicosis</td>
<td>22</td>
<td>1.01</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>21</td>
<td>0.97</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Epidermal cyst</td>
<td>16</td>
<td>0.74</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Trichilemmoma</td>
<td>16</td>
<td>0.74</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Facial granuloma</td>
<td>14</td>
<td>0.65</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>13</td>
<td>0.60</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Sebaceous hyperplasia</td>
<td>11</td>
<td>0.51</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Eczema</td>
<td>11</td>
<td>0.51</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

*a P < 0.0001*
lesions are treated with imiquimod, cryotherapy or photodynamic therapy. Moreover, the limitation of the study was the lack of dermoscopic descriptions and both clinical images and clinical diagnoses were based on experience of the referring physician. On the other hand, the patients were referred for punch, shave, or excisional biopsy from numerous public and private clinics. So, the analysis reflects a need for skin biopsy of the face in everyday life of dermatological practice and was not limited only to the academic settings.

It is important to underline the fact, that even in modern setting, with a standard help of dermoscopy and without easy access to confocal microscopy (which allows to reduce the number of diagnostic biopsies), there is still a high percentage of false-positive and negative cases that may be treated incorrectly in case of lack of collaboration with a dermatopathologist.

A suspicion of skin malignancy is the most common indication for biopsy from the lesions on the face. Because 10% of cases turned out to be inflammatory dermatoses, inflammatory entities should be also included in the differential diagnosis of the lesions on the face, especially in patients under 65 years of age. In most cases of skin tumors, the clinical diagnosis is confirmed by histopathological examination. In the case of inflammatory facial lesions, the accuracy of clinical diagnosis is lower, with a significant number of facial lesions appearing inflammatory in clinical evaluation but being diagnosed as skin cancers in pathology.

**References**


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**Table 4. The percentage of the correct diagnoses on the different regions of the face**

<table>
<thead>
<tr>
<th>Region of the face</th>
<th>Number of the correct diagnoses (%)</th>
<th>P value with the comparison to the other regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear</td>
<td>56/105 (53.33)</td>
<td>P = 0.734</td>
</tr>
<tr>
<td>Nose</td>
<td>417/725 (57.52)</td>
<td>P = 0.285</td>
</tr>
<tr>
<td>Lips</td>
<td>44/71 (61.97)</td>
<td>P = 0.253</td>
</tr>
<tr>
<td>Other regions (cheeks, forehead, chin)</td>
<td>698/1268 (55.05)</td>
<td></td>
</tr>
</tbody>
</table>

UV Irradiation of Nevi: Impact on Performance of Electrical Impedance Spectroscopy and a Convolution Neural Network

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Key words: electrical impedance spectroscopy, dermoscopy, convolution neural network, UV irradiation


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Introduction: UV irradiation of nevi induces transient melanocytic activation with dermoscopic and histological changes.

Objectives: We investigated whether UV irradiation of nevi may influence electrical impedance spectroscopy (EIS) or convolution neural networks (CNN).

Methods: Prospective, controlled trial in 50 patients undergoing phototherapy (selective UV phototherapy (SUP), UVA1, SUP/UVA1, or PUVA). EIS (Nevisense, SciBase AB) and CNN scores (Moleanalyzer-Pro, FotoFinder Systems) of nevi were assessed before (V1) and after UV irradiation (V2). One nevus (nevusirr) was exposed to UV light, another UV-shielded (nevusnon-irr).

Results: There were no significant differences in EIS scores of nevusirr before (2.99 [2.51-3.47]) and after irradiation (3.32 [2.86-3.78]; P = 0.163), which was on average 13.28 (range 4-47) days later. Similarly, UV-shielded nevusnon-irr did not show significant changes of EIS scores (V1: 2.65 [2.19-3.11], V2: 2.92 [2.50-3.34]; P = 0.094). Subgroup analysis by irradiation revealed a significant increase of EIS scores of nevusirr (V1: 2.69 [2.21-3.16], V2: 3.23 [2.72-3.73]; P = 0.044) and nevusnon-irr (V1: 2.57 [2.07-3.07], V2: 3.03 [2.48-3.57]; P = 0.033) for patients receiving SUP. In contrast, CNN scores of nevusirr (P = 0.995) and nevusnon-irr (P = 0.352) showed no significant differences before and after phototherapy.

Conclusions: For the tested EIS system increased EIS scores were found in nevi exposed to SUP. In contrast, CNN results were more robust against UV exposure.

ABSTRACT

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Conclusions: For the tested EIS system increased EIS scores were found in nevi exposed to SUP. In contrast, CNN results were more robust against UV exposure.
Introduction

Malignant melanoma accounts for the majority of skin cancer deaths and incidence remains at high levels in many countries of the world [1]. Thin melanomas are cured by surgical excision with a favorable prognosis. Hence, early diagnosis of melanoma is of utmost importance [1]. Although biopsy and histopathology remain the diagnostic standard, non-invasive diagnostic techniques are gaining importance [2]. Electrical impedance spectroscopy (EIS) has been evaluated as an adjunct tool for melanoma detection [3-6]. EIS applies alternating electric current and detects differences in the impedance between benign (well-organized) and malignant (more chaotic) tissues. Market approved EIS devices were shown to reach a sensitivity of more than 95% in melanocytic lesions [6]. Another promising non-invasive diagnostic technique is the assessment of dermoscopic images by artificial intelligence algorithms. To this end, deep learning convolutional neural networks (CNN) have been designed that work independently from predefined criteria and were shown to perform on, or even above, the level of trained dermatologists with regard to the classification of benign and malignant skin lesions [7-9].

Until today, skin cancer screenings that are assisted by the aforementioned diagnostic techniques have been offered throughout the entire year. However, even intermittent UV exposure was shown to induce transient melanocytic activation with morphological and histological changes [10, 11]. Dermoscopic features developing in UV exposed nevi include an increase in pigmentation and the appearance of black-brown globules [12, 13]. Histopathologic changes after UV exposition involve an increase in suprabasal melanocytes and an enhanced HMB45 expression [14]. In some cases UV-induced changes in benign nevi may be suggestive of malignant melanoma [15]. Thus, for clinicians it is an important question whether the diagnostic performance of EIS or CNN-based systems may be influenced by UV irradiation (eg during the summer months).

Objectives

The primary objective of this study was to assess the influence of UV irradiation on the diagnostic scores of an EIS system (Nevisense, SciBase AB) and of a CNN (MoleAnalyzer-Pro, FotoFinder Systems) when using these systems for examination of nevi. A secondary objective of this study was to address the reproducibility of EIS scores by performing 2 consecutive measurements for each lesion at each study visit.

Methods

This clinical study was performed in a prospective controlled setting at the Department of Dermatology, University of Heidelberg in 50 patients with 100 common nevi and a medical indication for phototherapy. The study was conducted in accordance with the Declaration of Helsinki principles (2013) and applicable local government regulations and independent Ethics Committee policies and procedures (ethics approval number S-279/2017).

Inclusion/Exclusion Criteria

Fifty patients scheduled for elective phototherapy with a minimum of 4 consecutive treatment sessions at our institution were included in this study. Participants had to be at least 18 years old and nevi needed to show the following characteristics: diameter between 2 mm and 20 mm; localized on intact skin without scarring, fibrosis, or other (inflammatory) skin conditions; not localized in hair-covered areas or special anatomic sites (i.e. acral skin, mucosa). We only included common nevi without any signs of malignancy.

Study Procedure

A total of 100 nevi in 50 patients were assessed by EIS. Dermoscopic images were acquired at each study visit. For each participant, 1 nevus (nevus_{irr}) was exposed to UV irradiation, whereas a second nevus (nevus_{non-irr}) was covered with an UV-shielding sticker. EIS scores were evaluated at 3 study visits: before the start of phototherapy (V1), during phototherapy (V2), after termination of phototherapy not earlier than 4 weeks following the last irradiation (V3). Nevus_{non-irr} was located in the same body area with similar size and shape as nevus_{irr} and was used as an intraindividual control to account for changes not attributable to direct UV irradiation. Moreover, at each study visit EIS scores of nevi were measured twice to assess the reproducibility. Since all studied nevi were not intended for histological assessment by protocol, the diagnosis of a benign nevus (ground truth) was based on expert consent (JKW, HAH, CF). Only clearly benign looking nevi were included; hence follow-up of nevi included the study visits performed and a common skin cancer screening thereafter.

UV Irradiation

Phototherapy was administered as part of clinical routine when indicated for treatment of diverse (inflammatory) skin diseases. Thus, the type of phototherapy was determined by the underlying skin condition and patient characteristics. Several treatments per week with increasing UV doses were administered. UVA1 phototherapy was performed with an UV-A1 lighting tube (Herbert Waldmann, spectral range 340–400 nm). SUP was administered with
a combination of UV-A and UV-B lighting tubes showing a spectral range of 280–400 nm (Herbert Waldmann). Psoralen-UV-A therapy (PUVA) was either performed as bath- or cream-PUVA-therapy (Herbert Waldmann, spectral range 315-400 nm).

**EIS Measurement**

EIS scores were measured with the market approved Nevisense device (Scibase AB). According to the manufacturer instructions the skin was moistened with physiological saline for 30 seconds and a reference measurement of healthy skin close to the lesion was obtained. The system computed a score (0-10) reflecting the degree of atypia identified and the validated cut-off of < 4 versus ≥ 4 was used to differentiate EIS-negative (benign) from EIS-positive (malignant) lesions.

**CNN Assessment**

Dermoscopic images were assessed by a marked approved deep learning CNN (MoleAnalyzer-Pro®, FotoFinder Systems) based on a modified version of a pretrained GoogleNet Inception v4 architecture [8]. The CNN computed malignancy scores (0-1) with a predefined threshold for malignancy at more than 0.5.

**Statistical Analysis**

Descriptive analyses were performed (frequency, mean, confidence intervals, range). For each nevus changes of EIS and CNN scores from visit 1 to 2 were assessed (intralesional differences). Additionally, for those nevi with measurements from all 3 visits changes of EIS and CNN scores from all timepoints were compared. Moreover, differences of scores between irradiated and non-irradiated lesions (nevus<sub>irr</sub> versus nevus<sub>non-irr</sub>) were studied per visit (interlesional differences). Non-parametric tests were applied to assess for statistical significance (Wilcoxon signed rank, Friedmann and McNemar). According to the predefined cut-offs for malignancy, diagnostic specificities were calculated. A linear mixed effects model with a compound symmetry structure was applied to assess whether UV irradiation had an effect on the difference in EIS scores at V1 and V2. Baseline EIS scores, age, gender, and irradiation (yes/no) were used as fixed factors. The patient ID was included as a random factor. To evaluate reproducibility of EIS measurements an intra-class correlation coefficient was calculated. P < 0.05 was considered statistically significant. SPSS Version 25 (IBM, SPSS) and R (R Core Team, 2021) together with the package nlme (Pinheiro, 2021) were used [16,17].

**Results**

**Patient Characteristics**

Patients (N = 50) were recruited between June 2017 and August 2018 (Table 1). Mean age was 54.4 years (range 22-75), 24 male and 26 female patients were included. Most patients received UV therapy for eczema (42%) or nodular prurigo (26%), some for granuloma annulare (12%), morphea (8%), lichen planus (4%), mycosis fungoides (4%) or others (4%). Forty-one patients showed skin type II, 1 patient skin type II-III and 8 patients skin type III. Common nevi with a network pattern and located on trunk or extremities were included. A total of 35 patients received SUP, 11 patients UVA1, 3 patients PUVA and 1 patient SUP and UVA1 in a sequence (Table 2). Most patients (70%) received SUP and a median dosage of 0.26 J/cm² UVB and 13 J/cm² UVA was administered. Considering the skin types of patients, these doses corresponded to about 3–4 minimal erythema doses (MED) of UVB and less than 1 MED-UVA administered over 7.7 sessions. [18]. Figure 1 depicts representative images of a patient nevi 1 and 2 from all 3 study visits with accompanying EIS and CNN scores.

**Assessment of EIS Scores**

Mean EIS score of the irradiated nevus<sub>irr</sub> slightly increased from 2.99 (2.51-3.47) at V1 to 3.32 (2.86-3.78) at V2 (Figure 2A). For patients attending V3 (N = 24) mean EIS score of nevus<sub>irr</sub> remained almost unchanged at

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics are depicted.</th>
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</thead>
<tbody>
<tr>
<td>Age in years (mean; range)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
</tr>
<tr>
<td>Skin condition, N (%)</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Nodular prurigo</td>
</tr>
<tr>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>Morphea</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Skin type, N (%)</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>II-III</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Localization nevus1/nevus2, N/N</td>
</tr>
<tr>
<td>Trunk</td>
</tr>
<tr>
<td>Upper extremities</td>
</tr>
<tr>
<td>Lower extremities</td>
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</table>
nor at V2 (P = 0.103, interlesional difference). Applying the predefined cut-off indicating malignancy (score ≥ 4), nevusirr was labeled “malignant” in 16 patients at V1 and in 20 patients at V2 (Figure 3). In contrast, nevusnon-irr was labeled “malignant” in only 12 patients at V1 and in 13 patients at V2. Paired assessment revealed no significant difference in the number of nevi labeled “malignant” at V1 versus V2, neither for nevusirr (P = 0.424) nor for nevusnon-irr (P = 1.0). For patients with measurements available from all 3 visits, EIS scores did not significantly vary between timepoints neither for nevusirr (P = 0.428) nor for nevusnon-irr (P = 0.719). Finally, when including all EIS measurements performed, the device achieved an overall specificity (true-negative rate) of 49.3%.

Regression Analysis Including EIS Scores
A linear mixed effects model was used to assess the impact of irradiation on the absolute and relative differences in EIS scores at V1 and V2 by comparing UV-irradiated versus shielded nevi. Here, irradiation was not a significant predictor (Table 3).

Reproducibility of EIS Measurements
We performed 2 consecutive EIS measurements for each nevus and visit to investigate reproducibility. Overall, 232 pairs of scores were recorded and the mean difference between consecutive scores was 0.06 (-0.27-0.4). The intraclass correlation coefficient was 0.653 (0.551-0.732). According to the definition of Cicchetti this corresponds to a good reliability, according to Koo/Li to a moderate reliability [19,20].

---

Table 2. Details on UV irradiation administered.

<table>
<thead>
<tr>
<th>UV irradiation, N</th>
<th>Patients N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUP</td>
<td>35</td>
</tr>
<tr>
<td>UVA1</td>
<td>11</td>
</tr>
<tr>
<td>SUP/UVA1</td>
<td>1</td>
</tr>
<tr>
<td>PUVA</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatments, N (mean; range)</th>
<th>7.7 (3-16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage (J/cm²) UVA (mean; SD)</td>
<td>13.0; 7.8</td>
</tr>
<tr>
<td>Dosage (J/cm²) UVB (mean; SD)</td>
<td>0.26; 0.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UVA1 Treatments, N (mean; range)</th>
<th>9.9 (3-15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage (J/cm²) UVA1 (mean; SD)</td>
<td>270; 140</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PUVA Bath/cream, N/N</th>
<th>2/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatments, N (mean; range)</td>
<td>12 (6-20)</td>
</tr>
<tr>
<td>Dosage (J/cm²) UVA (mean; SD)</td>
<td>6.6; 5.5</td>
</tr>
</tbody>
</table>

---

Figure 1. Nevus1 and nevus2 of a participating patient at all 3 study visits (V1-3) are depicted. From V1 to V2 nevusirr was irradiated with SUP during 10 appointments (cumulative dosage UVA 14.54 J/cm², UVB 0.29 J/cm²), whereas nevusnon-irr was UV-shielded. Corresponding electrical impedance spectroscopy (EIS) scores (0-10, top row) and convolution neural networks malignancy scores (0-1, bottom row) are depicted, scores marked in red illustrate a change in the diagnostic class, ie scores increased above the threshold for a malignant classification.
5 of the patients at V1, but in 2 patients at V2. Similarly, nevus non-irr was classified “malignant” in none of the patients at V1 but in 1 patient at V2. Paired assessments revealed no significant difference in the number of nevi classified “malignant” at V1 versus V2 neither for nevus irr (P = 0.5) nor for nevus non-irr (P = 1.0). When including patients with measurements available from all 3 visits, CNN scores were not significantly different between timepoints neither for nevus irr (P = 0.449) nor for nevus non-irr (P = 0.420). Finally, including all visits the rate of correct “benign” diagnoses was 94.7%.

Assessment by Type of Irradiation

Due to varying irradiation protocols a subgroup analysis was performed for the largest group of patients receiving SUP (N = 35). In this analysis mean EIS scores of nevus irr significantly increased from 2.69 (2.21-3.16) at V1 to 3.23 (2.72-3.73) at V2 (P = 0.044) and was 3.13 (2.40-3.84) for the 16 patients attending V3 (Figure 5). In parallel, mean

70 of the 232 (30.2%) pairs of scores a class change from < 4 to ≥ 4 or vice versa was found.

Assessment of CNN Scores

For 42 patients dermoscopic images were available from V1 and V2. Mean CNN scores of nevus irr were 0.06 (0.03-0.1) at V1, 0.06 (0.02-0.11) at V2, and 0.11 (-0.02-0.23) for the 15 patients with images available from V3 (Figure 4). Mean CNN scores of nevus non-irr were 0.05 (0.02-0.08) at V1, 0.04 (0.01-0.07) at V2, and 0.15 (0.05-0.25) at V3 (Figure 4). First, we statistically compared CNN scores before and after irradiation (V1 versus V2). There were no significant differences in CNN scores at V1 versus V2 neither for nevus irr (p = 0.995, intralesional difference) nor for nevus non-irr (P = 0.352, intralesional difference). Additionally, we found no significant differences in CNN scores of nevus irr versus nevus non-irr at V1 (P = 0.703, interlesional difference) and V2 (P = 0.675, interlesional difference). According to the predefined CNN threshold for malignancy, nevus irr was classified “malignant” in none of the patients at V1, but in 2 patients at V2. Similarly, nevus non-irr was classified “malignant” in none of the patients at V1 but in 1 patient at V2. Paired assessments revealed no significant difference in the number of nevi classified “malignant” at V1 versus V2 neither for nevus irr (P = 0.5) nor for nevus non-irr (P = 1.0). When including patients with measurements available from all 3 visits, CNN scores were not significantly different between timepoints neither for nevus irr (P = 0.449) nor for nevus non-irr (P = 0.420). Finally, including all visits the rate of correct “benign” diagnoses was 94.7%.

Figure 2. Boxplots show electrical impedance spectroscopy (EIS) scores of irradiated nevus irr and UV-shielded nevus non-irr at all 3 study visits (V1-before UV irradiation; V2-after UV irradiation; V3-not earlier than 4 weeks following the last irradiation). The upper and lower bounds of boxes represent the 25th and 75th percentiles while the median is given by the line intersecting both boxes. Whiskers present the full range of malignancy scores. The a priori cut-off for a malignant classification is indicated by dotted lines (EIS score ≥ 4).
scores at V1 versus V2, neither for nevus_{irr} (P = 0.344) nor for nevus_{non-irr} (P = 0.388).

For 30 patients CNN scores were available, there was neither a significant difference in CNN scores between V1 and V2 for nevus_{irr} (P = 0.797) nor nevus_{non-irr} (P = 0.894).

**Table 3.** A linear mixed-effects model was used to assess the impact of irradiation on the absolute in electrical impedance spectroscopy scores at V1 and V2 (before and after irradiation) by comparing UV-irradiated versus shielded nevi.

<table>
<thead>
<tr>
<th></th>
<th>Estimates</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.43</td>
<td>0.12; 2.74</td>
<td>0.037</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>-0.01; 0.03</td>
<td>0.479</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.30</td>
<td>-0.31; 0.91</td>
<td>0.347</td>
</tr>
<tr>
<td>EIS score at V1</td>
<td>-0.57</td>
<td>-0.73; -0.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Irradiation (no)</td>
<td>-0.25</td>
<td>-0.69; 0.18</td>
<td>0.254</td>
</tr>
</tbody>
</table>

CI = confidence interval; EIS = electrical impedance spectroscopy.

**Table 4.** A linear mixed-effects model was used to assess the impact of irradiation on the relative differences in electrical impedance spectroscopy scores at V1 and V2 (before and after irradiation) by comparing UV-irradiated versus shielded nevi.

<table>
<thead>
<tr>
<th></th>
<th>Estimates</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.88</td>
<td>0.02; 1.74</td>
<td>0.050</td>
</tr>
<tr>
<td>Age</td>
<td>0.01</td>
<td>-0.01; 0.02</td>
<td>0.502</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.41</td>
<td>0.01; 0.81</td>
<td>0.053</td>
</tr>
<tr>
<td>EIS score at V1</td>
<td>-0.32</td>
<td>-0.43; -0.21</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Irradiation (no)</td>
<td>-0.18</td>
<td>-0.46; 0.10</td>
<td>0.221</td>
</tr>
</tbody>
</table>

CI = confidence interval; EIS = electrical impedance spectroscopy.
and after phototherapy with different irradiation protocols performed. We found that for the overall group of patients and across all phototherapy regimen EIS scores of both UV irradiated and UV-shielded nevi were not significantly different before and after UV exposure. There may be several explanations for this observation, which are not mutually exclusive. In agreement with others we found a limited reproducibility of EIS measurement [21]. This might have probably interfered with the statistical comparison of EIS scores before and after UV exposure (background analytical noise covering relevant signals). Second, cumulative UV doses until the second visit (V2) might not have been sufficient to induce significant alteration of EIS scores. Yet, morphological changes in nevi have been reported as early as after 2 MED [12]. After two UVB minimal erythema doses marked melanocytic activation was reported, avoided by physical and sunscreen protection [22]. Another study found that even after a single dose of UVB clinical and dermoscopic changes in nevi occurred, partially prevented by physical barriers or sunscreens [23]. Moreover, a positive correlation of the extent of morphological changes with increasing total

Conclusions

Dermoscopic and histopathologic changes of nevi following UV irradiation have previously been described [12, 14]. Such changes may be of clinical relevance when patients attend skin cancer screenings following sun exposure. Particularly for patients under follow-up by sequential digital dermoscopy subtle changes related to sun exposure, e.g., increase in the number of dark dots and globules, may result in an increased number of unnecessary excisions. Hence, another short time follow-up examination before biopsy of melanocytic lesions has previously been recommended after intense UV exposure [12].

According to our literature search, there is no data available on the performance of assistant devices such as EIS or CNN when used to assess melanocytic lesions after sun exposure. Our study provides first data on EIS and CNN scores of common nevi before and after phototherapy.

Overall, 50 patients were included to assess EIS scores of 2 nevi per patient (UV irradiated and UV shielded) before and after phototherapy.
EIS scores at V2 for both UV irradiated and shielded nevi. In our study the increase in EIS scores was quite similar for directly versus indirectly (because UV-shielded) irradiated nevi, which is in line with previous studies reporting melanocyte activation and proliferation after irradiation in both UV exposed and shielded human skin [25,27]. It has been postulated that mediators from irradiated skin might spread to neighboring UV protected skin through a paracrine pathway [25,27,29]. In confirmation, our linear effects model assessing EIS scores before and after irradiation did not reveal an impact of direct UV irradiation.

From our results we assessed the rate of nevi correctly labeled as benign by means of EIS scores (true negative rate, specificity). EIS attained a true negative rate of roughly 50%, which appears low in nevi lacking any dermoscopic signs of malignancy. This finding is in line with previous studies on EIS reporting a limited specificity of 34.4% at a high sensitivity of 96.6% [5,6]. Due to the study setting malignant lesions were not included, and thus we could not calculate sensitivity (true positive rate). The specificity of 49.3% obtained in the study is still superior to the 34.4% reported in the pivotal study with the method. This difference might be cumulative UV dose has also been shown [24]. Finally, it seems well conceivable, that “moderately” UV exposed nevi have been included in the training data of the device [6], which might have attenuated effects on EIS scores, and particularly on class changes (changes from benign to malignant after UV exposure). In contrast, effects of acute sun exposure were not further assessed in pivotal studies since exclusion criteria of the pivotal study included “lesions and/or reference located on acute sunburn”. In the future, training sets of devices for the evaluation of melanocytic lesions should consider the influence of UV irradiation. The information that sun-exposed lesions were excluded from studies has to be included in clinical tutorials for users and in the webpage of the device.

In the literature changes of melanocytic lesions have been reported following exposure to UV light of various wavelengths [12,13,25-27]. Although natural sunlight differs from therapeutic irradiation [28], SUP includes both the UVB and UVA component and thus a subgroup analysis was performed for this largest group of patients. SUP patients received a dose of 3-4 MED-UVB over a mean number of 7.7 sessions. In these cases, we found a significantly elevated EIS scores at V2 for both UV irradiated and shielded nevi. In our study the increase in EIS scores was quite similar for directly versus indirectly (because UV-shielded) irradiated nevi, which is in line with previous studies reporting melanocyte activation and proliferation after irradiation in both UV exposed and shielded human skin [25,27]. It has been postulated that mediators from irradiated skin might spread to neighboring UV protected skin through a paracrine pathway [25,27,29]. In confirmation, our linear effects model assessing EIS scores before and after irradiation did not reveal an impact of direct UV irradiation.

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explained by the different populations of patients and lesions included within the two studies, since the accuracy of EIS was shown to be correlated with lesion atypia. For a comparison, the ABCD rule of dermoscopy achieves a specificity of 91.2% and a true negative predictive value of 95.8% [30], hence surpassing EIS by far.

We used this prospective clinical study to additionally assess the reproducibility of EIS scores (2 consecutive measurements of the same lesions). One previous publication raised concerns regarding reproducibility, because the authors found that for 45% of benign lesions the difference in EIS scores was ≥2 points and differences up to ≥4 points were observed. Moreover, for one melanoma included in their study a decrease in EIS scores by 2 points was found after repeated measures [4]. According to the correlation coefficient in our study, reproducibility was “good” to “moderate”, depending on the thresholds applied [19, 20]. Yet, for approximately 30% of repeated measurements a change in the diagnostic category (from benign to malignant or vice versa) was observed, which in our view is an important limitation regarding clinical application of EIS. There are various factors which determine electrical impedance during the EIS procedure, amongst others the amount of saline solution applied to the skin. The intralesional variability of EIS scores may be explained by the intrinsic variability of the method, but possibly also by a modification of the lesion by repeated application of the liquid and electrodes on the skin surface in a short period.

Besides EIS measurements, we assessed dermoscopic images by a deep learning CNN for a second approach based on lesion morphology. Here, we found no relevant changes of CNN scores following UV irradiation, which implies a favorable robustness of the applied CNN. The rate of correctly classified benign lesion was 94.7%, which is in line with its previously published high specificity [8, 9]. The CNN was trained with >150,000 labeled dermoscopic images from around the globe comprising a real-life sample of nevi with or without previous sun exposure. In our study CNN scores of included nevi were quite low, reflecting our study setting with inclusion of clinically clear-cut benign nevi. Since only common nevi were included, we may not draw any conclusions with regard to atypical nevi or melanomas.

Altogether, our study reveals several further limitations. The number of included patients was low and only artificial sources of UV irradiation were assessed [31]. Furthermore, the applied phototherapy protocols varied with regard to UV spectrum, applied dosage and number of sessions.

In conclusion, our study shows that UV exposure may increase EIS scores of nevi. UV shielded nevi surrounded by UV exposed skin showed similar changes as directly irradiated nevi. Physicians should be aware of these interrelations when applying EIS as an assistance system. In contrast, the tested CNN was more robust to the effect of UV exposure with almost unchanged scores.

References


Challenges for New Adopters in Pre-Surgical Margin Assessment by Handheld Reflectance Confocal Microscope of Basal Cell Carcinoma; A Prospective Single-center Study

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Key words: reflectance confocal microscopy, basal cell carcinoma, micrographic Mohs surgery, margin control


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Introduction: In vivo reflectance confocal microscopy (RCM) is a useful tool for assessing pre-surgical skin tumor margins when performed by a skilled, experienced user. The technique, however, poses significant challenges to novice users, particularly when a handheld RCM (HRCM) device is used.

Objectives: To evaluate the performance of an HRCM device operated by a novice user to delineate basal cell carcinoma (BCC) margins before Mohs micrographic surgery (MMS).

Methods: Prospective study of 17 consecutive patients with a BCC in a high-risk facial area (the H zone) in whom tumor margins were assessed by HRCM and dermoscopy before MMS. Predicted surgical defect areas (cm²) were calculated using standardized photographic digital documentation and compared to final defect areas after staged excision.

Results: No significant differences were observed between median HRCM-predicted and observed surgical defect areas (2.95 cm² [range: 0.83–17.52] versus 2.52 cm² [range 0.71–14.42]; P = 0.586). Dermoscopy, by contrast, produced significantly underestimated values (median area of 1.34 cm²)
Introduction

Basal cell carcinoma (BCC) is the most common skin cancer and its incidence is rising worldwide due to chronic UV exposure and aging [1]. While the vast majority of BCCs at sites such as the trunk and extremities can be removed by simple excision or local destructive therapies, tumors located in high-risk areas such as the H zone (central area of the face, around the eyes, nose, lips, and ears) are at greater risk of destructive local spread and recurrence. Effective surgical treatment is essential for guaranteeing tumor-free margins and maximal functional and cosmetic outcomes in BCCs that are clinically ill defined and those in high-risk areas, with an aggressive histologic subtype (micronodular, morpheaform, basosquamous, infiltrative), or a history of incomplete excision.

Mohs micrographic surgery (MMS) with rapid intraoperative histologic confirmation of full tumor margins offers the highest success rates in the excision of facial BCCs [2]. MMS, however, requires advanced surgical and histopathologic skills and support from histotechnicians with experience in this procedure. There may also be financial and resource-related obstacles. Reflectance confocal microscopy (RCM) might facilitate BCC margin mapping prior to MMS as it can be used to delineate lateral tumor margins that cannot be determined clinically or by dermoscopy [3,4]. Studies of the use of RCM in this setting, however, have involved users with more than 5-years experience in image navigation and interpretation [3,5-9]. In addition, most of the lesions investigated were located on flat, even surfaces on the face or trunk, where natural skin folds and bony prominences, such as those found in the H zone, do not interfere with navigation. With the recent approval of new Current Procedural Terminology (CPT) codes for RCM imaging and evaluation in the United States and the advent of lower-cost RCM devices, the number of users is expected to increase [10,11].

Conclusions

Even in the hands of a novice user, HRCM is more accurate than dermoscopy for delineating lateral BCCs margins in high-risk areas and performs well at predicting final surgical defects.

Objectives

The aim of this study was to investigate the performance of a handheld RCM (HRCM) device operated by a user with 1-year experience in this technique for lateral margin assessment in BCCs in high-risk locations in a real-life clinical setting.

Methods

We prospectively included consecutive patients with non-pigmented, ill-defined, biopsy-proven BCCs located in high-risk areas of the face treated with MMS at our dermatology department between August 2020 and September 2021. The study was approved by the hospital ethics committee, and informed written consent was obtained from all participants prior to enrolment. The study was conducted according to the principles of the Declaration of Helsinki.

The target lesions were imaged using the Vivascope 3000 HRCM device (MAVIG/Caliber ID), which has a horizontal resolution of ~1 μm, optical sectioning of ~3 μm, and a field of view of 0.75 x 0.75 mm. The images were captured in vivo before surgery by an investigator (NR) with 1-year experience who had attended an RCM course and received 2 months practical training at a reference unit.

The clinical margins were first determined by dermoscopy and marked on the skin using a silver paint marker (Edding 780 creative 0.8 mm, Edding International. These markings facilitated RCM navigation and margin calculation since silver ink can be visualized by RCM [6]. The margins were then determined using HRCM and the original silver markings readjusted to the distance of one field of view (0.75 x 0.75) between the last inside tumor island to the internal side of the silverpen delineation. Using a method previously described by a member of our team (OY) [12], we produced standardized photographic documentation containing digital images of the lesions before and after dermoscopy, before and after RCM, and during and after MMS. These images were then calibrated in ImageJ (NIH, available from http://image.nih.gov/ij/) using anthropometric measurements and a surgical ruler placed in the image field. The same software was used to calculate surgical defect areas predicted by dermoscopy and HRCM. A 3-mm margin was added to
the predicted values as the MMS protocol at our hospital requires histologic clearance of at least 3 mm. Images of the final surgical defect were obtained before surgical reconstruction and the area was re-measured to compare it with the dermoscopy- and HRCM-predicted areas.

The surgeons who performed MMS (AJ, JB, GC) were blinded to the dermoscopy and HRCM calculations, and, as per protocol, extended the dermoscopic margin by 3 mm during the first excision stage. The excised specimen was frozen and sectioned for microscopic examination of lateral and deep margins and, where necessary, the process was repeated until achievement of full histologic clearance.

Statistical Analysis

Descriptive statistics were used to describe the characteristics of the cohort, lesion size, and predicted and observed surgical defect areas. Normal distribution was checked using the Kolmogorov-Smirnoff test. Since most of the variables were non-normally distributed, non-parametric tests were used. The Wilcoxon test was used to compare the final surgical defect area and the areas predicted by dermoscopy and HRCM. All analyses were performed in SPSS version 22 (IBM corporation).

Results

Seventeen consecutive patients (9 men and 8 women) agreed to participate in the study and underwent complete BCC excision by MMS (Table 1). The median age at the time of HRCM examination was 70 years (range: 46–86 years). Thirteen tumors were located on the nose, 2 on the temple, and 1 each on the ear and inner canthus of the eye (Figure 1). Four patients had previously undergone conventional surgery at the same site and had had positive margins or experienced recurrence. Another 4 patients had been treated with cryotherapy, curettage, or topical imiquimod and 2 had undergone radiotherapy. Salvage MMS was performed in one patient in whom oral vismodegib had been discontinued after 4 months due to adverse effects. Fourteen patients (82.3%) had an infiltrative BCC component on histology, 2 had a nodular/superficial subtype, and 1 had a superficial, undetermined subtype (Table 1).

A median of 2 MMS stages (range: 1–4) were needed to achieve tumor-free margins after margin delineation with dermoscopy (Table 1). Dermoscopy underestimated the final surgical defect area by a median of 1.18 cm² (1.34 cm² [range: 0.41–4.64] versus 2.52 cm² [range: 0.71–14.42]; P < 0.001). There were no statistical differences between the HRCM-predicted area and the final area (2.95 cm² [range: 0.83–17.52] versus 2.52 cm² [range: 0.71–14.42]; P = 0.586). HRCM, however, overestimated defect size in three cases and underestimated it in four (Figure 2). Of the 3 patients with overestimated defect areas, 1 had been previously treated by radiotherapy (patient #12), another had a purely infiltrative component (patient #14), and another had prominent sebaceous hyperplasia mistaken for tumor islands by the confocalist (patient #3). Of the 4 patients with underestimated defect areas, 1 had been treated with conventional surgery (patient #11), 1 with curettage (patient #16), 1 with radiotherapy (patient #9), and 1 with imiquimod (patient #5). These treatments had resulted in scarring at different levels of the epidermis and/or dermis.

Conclusions

The main limitation of this study is its small sample size (17 consecutive patients), which was partly due to the COVID-19 pandemic, as fewer operations were performed and fewer patients agreed to participate in the study due to fear of infection by severe acute respiratory syndrome coronavirus 2. Another notable limitation is the decreased resolution offered by RCM at depths of greater than 200–250 μm. Deep margin assessment with this technique is thus suboptimal, particularly for purely infiltrative tumors, deep tumors, and tumors located under scar tissue [13]. Finally, since this was a real-life bedside study involving live imaging, we were unable to assess the difficulty of each case and compare the performance of the novice confocalist with that of an expert. Another limitation is that there is yet no follow-up of the cases available.

The use of in vivo RCM imaging for the bedside diagnosis and histologic subtyping of BCC and other skin cancers has gained popularity in the past decade [13-15]. Its usefulness in the assessment of lateral margins has been demonstrated in nodular and superficial BCCs located on flat surfaces such as the cheek, forehead, and trunk [3,5,6]. Candidates for MMS, however, usually have lesions in high-risk areas of the face, where performance of wide-probe RCM is complicated by skin elasticity and the presence of concave and convex surfaces. HRCM, by contrast, offers advantages in uneven locations, as it allows for free-form navigation. It also presents challenges, however, especially for new users working in real-life settings, as unlike wide-probe RCM, it does not have mosaicking capabilities. Image acquisition is therefore heavily user dependent.

This prospective study analyzed the use of HRCM in the assessment of BCC margins prior to MMS in clinical practice at a single institution. Our results suggest that, even in the hands of novice operators and in challenging locations such as the nose, HRCM outperforms dermoscopy. In more complex cases, however, such as tumors previously treated with radiotherapy, surgery, or imiquimod, it may produce less accurate results due to the presence of scar tissue impeding visualization of tumor structures. Other difficulties include recognition of infiltrative BCC components or BCC...
<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (y)</th>
<th>BCC location</th>
<th>BCC subtype</th>
<th>Treatment before RCM</th>
<th>Dermoscopy-predicted surgical defect area (cm(^2))</th>
<th>HRCM-predicted surgical defect area (cm(^2))</th>
<th>Final surgical defect area (cm(^2))</th>
<th>No. of MMS stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>83</td>
<td>Nasal tip</td>
<td>Nodular/infiltrative</td>
<td>Surgery in 2012, vismodegib for 4 months in 2017</td>
<td>4.727</td>
<td>4.687</td>
<td>4.364</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>42</td>
<td>Nasal ala</td>
<td>Nodular/adenoid/micronodular</td>
<td>Surgery with positive margins in 2019</td>
<td>1.082</td>
<td>0.803</td>
<td>0.818</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>86</td>
<td>Nose</td>
<td>Superficial multifocal/nodular/infiltrative</td>
<td></td>
<td>2.114</td>
<td>4.148</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>76</td>
<td>Nose</td>
<td>Superficial/nodular</td>
<td></td>
<td>2.191</td>
<td>3.326</td>
<td>3.468</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>Tip/dorsum of nose</td>
<td>Superficial multifocal/nodular</td>
<td>Imiquimod</td>
<td>3.614</td>
<td>2.718</td>
<td>3.968</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>68</td>
<td>Nasal ala</td>
<td>Infiltrative/micronodular</td>
<td></td>
<td>2.725</td>
<td>2.947</td>
<td>2.874</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>84</td>
<td>Ear</td>
<td>Nodular/infiltrative</td>
<td>Cryotherapy</td>
<td>2.149</td>
<td>2.249</td>
<td>2.125</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>71</td>
<td>Nose</td>
<td>Infiltrative</td>
<td></td>
<td>1.72</td>
<td>1.87</td>
<td>1.794</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>70</td>
<td>Nasal ala</td>
<td>Infiltrative/micronodular</td>
<td>Radiotherapy</td>
<td>2.612</td>
<td>3.261</td>
<td>7.647</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>82</td>
<td>Nose</td>
<td>Infiltrative/superficial/nodular</td>
<td>Curettage + electro-coagulation</td>
<td>6.559</td>
<td>5.379</td>
<td>7.124</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>52</td>
<td>Nasal tip</td>
<td>Superficial/undefined</td>
<td>Radiotherapy</td>
<td>0.977</td>
<td>6.83</td>
<td>0.71</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>68</td>
<td>Nasal ala</td>
<td>Macronodular</td>
<td></td>
<td>2.509</td>
<td>2.505</td>
<td>2.357</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>73</td>
<td>Temple</td>
<td>Micronodular/infiltrative</td>
<td></td>
<td>5.13</td>
<td>17.519</td>
<td>14.416</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>78</td>
<td>Nasal tip</td>
<td>Infiltrative/micronodular</td>
<td></td>
<td>1.044</td>
<td>1.06</td>
<td>1.105</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>60</td>
<td>Inner canthus of eye</td>
<td>Infiltrative</td>
<td>Surgery in 2020</td>
<td>1.753</td>
<td>1.832</td>
<td>2.52</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>53</td>
<td>Nasal ala</td>
<td>Infiltrative</td>
<td></td>
<td>1.106</td>
<td>1.115</td>
<td>1.03</td>
<td>1</td>
</tr>
</tbody>
</table>

BCC = basal cell carcinoma; F = female; HRCM = handheld reflectance confocal microscopy; M = male; MMS = micrographic Mohs surgery.
mimickers, such as sebaceous hyperplasia, hair follicles, and eccrine glands (Table 2). Novice users need to be familiar with normal skin structures and aware of the limitations of HCRM. We believe that image-reading challenges can be overcome by ensuring that training programs, in addition to focusing on pathologic characteristics of tumors, include content on normal skin structures, mimickers, and RCM limitations. This knowledge should shorten the learning curve. Rapid feedback from experienced confocalists via image-sharing platforms in cases of doubt could also be very valuable. Scouting biopsies are useful in complex cases as they can help differentiate tumors from benign structures or scar tissue, especially when working at depths of greater than 200-250 µm. A summary of the above challenges and proposed solutions is given in Table 2.

Although HRCM has cellular resolution, it presents some technical challenges. Navigation in the horizontal plane, for example, can be problematic due to loss of reference points and the impossibility of building an overall mosaic of the lesion. Visualization thus is restricted to a small field of vision (0.75 x 0.75 mm or 1 x 1 mm depending on the generation of microscope). Patient breathing and movement can

Figure 1. Locations of basal cell carcinomas (red circles) included in the study. High-risk areas are shown in orange.

Figure 2. Representative cases of basal cell carcinoma (BCC) showing good agreement between surgical defect areas predicted by handheld reflectance confocal microscopy (HRCM) and the defect areas after Mohs micrographic surgery (MMS) (A-D), overestimated defect areas (E-H), and underestimated defect areas (I-L). (A) Similarity between the HRCM-predicted surgical defect area (blue line) and the final area (B) in a BCC with evident tumor islands seen by RCM (C) and a nodular subtype identified in the intraoperative frozen section (D). (E) HRCM-predicted surgical defect area in a BCC previously treated with radiotherapy that was significantly larger than the final defect area after MMS (F). HRCM images of radiation-induced dermal fibrosis (G) were mistaken for collagen surrounding deep tumor islands, but these were ruled out by histology (H). The HRCM–predicted surgical defect area in (I) was significantly smaller than the final area (J) in a superficial, infiltrative BCC visible by HRCM (K) and histology (L).
Table 2. Basal cell carcinoma margin delineation by HRCM: limitations, challenges for new users, and proposed solutions.

<table>
<thead>
<tr>
<th>Image-reading challenges/limitations</th>
<th>Proposed solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative subtypes (no clear tumor islands or clefting but dark silhouettes that appear as imprints embedded in bright collagen)</td>
<td>Training in image reading, scouting biopsies, combined use of OCT, platforms for consulting with RCM experts</td>
</tr>
<tr>
<td>Limited penetration depth for delineating deep margins</td>
<td>Combined use of OCT to explore vertical planes</td>
</tr>
<tr>
<td>Prominent sebaceous hyperplasia, hair follicles, and eccrine glands that can be mistaken for tumor islands in facial BCC</td>
<td>Training in image reading, scouting biopsies, platforms for consulting with RCM experts</td>
</tr>
<tr>
<td>Tissue distortion due to previous biopsies and treatments</td>
<td>Training in image reading, scouting biopsies</td>
</tr>
</tbody>
</table>

Technical challenges associated with horizontal plane navigation

<table>
<thead>
<tr>
<th>Proposed solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of reference points due to small field of vision (0.75 x 0.75 mm or 1 x 1 mm) and lack of automated mosaicking capabilities</td>
</tr>
<tr>
<td>Image distortion due to patient breathing and movement</td>
</tr>
<tr>
<td>Loss of direct contact with HRCM device over natural skin folds and bony prominences</td>
</tr>
</tbody>
</table>

FOV = field of view; HRCM = handheld reflectance confocal microscopy; OCT = optical coherence tomography; RCM = reflectance confocal microscopy.

also result in abrupt motion changes that can distort images. Distortion can also occur when navigating skin folds or bony prominences where it is impossible to establish a flat contact (Table 2). Newer multimodal systems such as combined RCM and optical coherence tomography (OCT) and line-field confocal OCT allow for deeper tissue imaging and improved accuracy in the delineation of lateral and deep tumor margins [10,17]. The problem of reference point loss could be overcome by using in vivo wide-field imaging to guide the horizontally moving device over the skin surface (Table 2) [18]. HRCM video-mosaicking can also be used to create static images from dynamic videos, enabling improved navigation and interpretation and facilitating comparisons between confocalists [8,12,19]. A subsequent image processing step is necessary, however, as in vivo video-mosaicking is not currently available in native HRCM software. Other options for more precise imaging over uneven surfaces include the use of robotics or HRCM devices with a smaller optical lens for improved skin contact.

Although the number of RCM users is growing worldwide and will continue to grow following the recent approval of RCM CPT codes in the United States, expert users are still limited in number. We have shown that an HRCM device operated by a novice user in real-life clinical practice performs well in the presurgical assessment of BCC margins. We have also offered some suggestions on how performance can be further improved. RCM users often receive limited training in image acquisition and interpretation. They typically learn by experience and feedback (based on pathology reports, for example). While this also has positive effects, the learning curve could be shortened by designing certificate training courses and mentoring programs, establishing image-sharing platforms for consultations between novice and experienced users, and integrating novel technical advances, such as multimodal imaging and artificial intelligence. Nevertheless, our findings show that, even in difficult conditions, HRCM operated by a single, novice user, performed well in the delineation of BCC margins and provided very useful data for application in everyday clinical practice.

References


Dermoscopy and Reflectance Confocal Microscopy to Estimate Breslow Index and Mitotic Rate in Primary Melanoma

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Key words: melanoma, confocal microscopy, mitotic rate, Breslow index, prognostic markers


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Non-invasive imaging techniques offer the possibility to optimize the first approach to melanoma. Reflectance Confocal Microscopy (RCM) has a promising role in predicting the main prognostic events in the dermo-epidermal and papillary dermis.

Objectives: To identify pre-surgical criteria that can predict the main prognostic features of melanoma.

Methods: A retrospective cohort-study evaluated dermoscopic, confocal and histopathological characteristics of consecutively diagnosed sporadic melanomas. RCM-melanoma patterns classified into 1) dendritic-cell, 2) round-cell, 3) dermal nest and 4) combined type. Acral, facial and mucosal locations were excluded.

Results: Ninety-two primary melanomas were included: 44 males and 48 females (mean age 60.4 years, standard deviation [SD] 16.2) with a mean Breslow of 1.43 mm (SD 1.6). The most frequent
Introduction

Currently, the 10-year cause-specific survival rate of patients diagnosed with localized cutaneous melanoma (that is, in the absence of nodal or visceral involvement) varies from 75% to 98% [1]. Promising results from molecular profiling of melanoma will shed some light on the prognostic classification of primary tumors [2]; the revised 8th version of AJCC, however, considers that the main prognostic markers of cutaneous melanoma are still ulceration and Breslow depth index of the primary tumor. Mitotic rate is no longer included in the current AJCC; nevertheless, the Melanoma Expert Panel recognizes mitotic rate as an important prognostic parameter to predict sentinel lymph node status and outcome in N0 stage [3].

The prediction given by the prognostic markers prior to removing the tumor could 1) optimize the first approach to the patient: devising an accurate surgery plan and indications for staging tests, and 2) help to preserve fresh samples for further molecular studies in the areas of interest.

Dermatological non-invasive imaging techniques have opened a new era of in vivo tumor characterization. Dermoscopically, several attempts have been made to predict mitotic and Breslow indexes, and even the sentinel lymph node status, based on the various in vivo morphologic features of primary melanoma [4-6].

Reflectance confocal microscopy (RCM) provides real-time evaluation of skin by generating horizontal optical sections from the epidermis to the papillary dermis with cellular-level resolution. Multiple studies have demonstrated not only the high correlation of dermoscopic and confocal features with histopathology, but also the impact of RCM on melanoma diagnostic accuracy - an ancillary tool to dermoscopy, especially with challenging and amelanotic tumors [7-11]; and in a recent Chochrane systematic review, RCM demonstrated may have a potential role in the assessment of lesions that are difficult to diagnose using visual inspection and dermoscopy alone [12].

Additionally, four different RCM melanoma patterns have been described in order to classify melanomas based on their cytology and architectural morphology: 1) dendritic-cell melanomas, 2) round-cell melanomas, 3) dermal nest melanomas and 4) combined type (that may represent an evolution of the other three types) [13,14].

Objectives

Beyond the morphological classification of primary tumors, the goal of the present study was to identify pre-surgical dermoscopic and confocal features of primary tumors that can be correlated with prognostic markers in localized cutaneous melanoma.

Methods

A retrospective cohort study of consecutively pathologically proven cutaneous melanomas diagnosed in a referral unit was conducted. Inclusion criteria stipulated available tumors with high quality clinical, dermoscopic and confocal images prior to excision, and pathological samples to re-review. Only sporadic cases of melanoma were included. Mucosal, acral and facial locations were excluded. The inclusion period was from February 2011 to February 2015.

Stored high-resolution clinical-dermoscopy images were obtained by Canon G11 and DermLite® photo (3 GEN, LLC). RCM images obtained by Vivascope 1500 (Lucid Inc.) included a minimum of three mosaics on a horizontal plane (“VivaBlock” modality) covering a maximum area of 7 mm², acquired in the spinous-granular layer, the dermal-epidermal junction and the upper dermis respectively. Furthermore, several confocal sections at 500 x 500 microns with vertical montage images (stack images) from stratum corneum to papillary dermis (maximum depth achieved, 250 µm) were acquired in the areas of interest.

Based on the literature, twenty clinical-dermoscopic criteria, including a quantitative Total Dermoscopy Score (TDS) [15], the 7-checkpoint list [16] and 22 confocal features, were established. Confocal characterization of primary melanomas according to the Pellacani et al classification and the confocal Barcelona algorithm, were also assessed [9,13].

dermoscopic presentation was the multicomponent pattern, the predominant confocal pattern was dendritic-cell type (44.6%). The presence of pigmented network on dermoscopy was related to lower Breslow and mitotic rates (both P = 0.002); in contrast to the presence of visible vessels, which was related to higher Breslow and mitotic indexes (both P = 0.001). Confocal observation of dermal nests or atypical cells in the papillary dermis was related to a higher mitotic rate (P = 0.006 and P = 0.03, respectively). Similarly, diffuse inflammatory infiltrates visible in the superficial dermis was associated with higher Breslow (P = 0.04) and mitotic index (P = 0.04).

Conclusions: Dermoscopic and RCM in vivo findings on primary melanoma correlate with histopathologic Breslow index, mitotic rate and tumor infiltrating lymphocytes. The architecture and cytology of primary melanoma can be estimated by combining dermoscopy and RCM prior to excision.
In addition, confocal features were evaluated according to
the percentage of the lesion surface that each presented: 25%, 50%, 75% or 100% of the lesion. For the histological
review, 12 histological routine features were evaluated
(Breslow, ulceration, radial or vertical growth phase, mitotic
index per mm$^2$, and also 4 characteristics described by Vios
et al [17]: nesting or scatter growth, pigmentation and cell
shape (summarized in Tables 2 and 3). The Hospital Clinic
Ethics Committee approved the protocol and all procedures
followed the principles of the Declaration of Helsinki.

### Statistical Analysis

SPSS Statics for Windows, version 22.0 (IBM Corp. Released
2013) was used to assess: descriptive values of all qualitative
variables by Pearson’s Chi Square test; quantitative (age, size
of lesions, dermoscopic and confocal scores, and Breslow
index) and semi-quantitative scales (such as mitosis, regres-
sion, nesting, pagetoid extension) by Student t-test. Com-
parisons between categorical variables and the correlation
between them were analyzed using Pearson’s chi-square and
Fisher exact test when any cell had an expected count of less
than 5. For quantitative continuous variables, Student t-test
was used for comparison between two groups and ANOVA
where more than two were compared. Person coefficient was
used to study the correlation between variables and Spear-
man correlation coefficient if nonparametric applicability
conditions were not reached. The level of statistical signif-
icance was set at bilateral 5%. The linear regression model
was applied to identify independent markers among quanti-
tative variables.

### Results

From the 132 patients who were initially included, 40 were
excluded due to poor quality of images or the unavailability
of histopathologic samples for reevaluation. All 92 patients
were finally included with demographics and clinical staging
collected from their medical records.

### Clinical-dermoscopic Attributes

In total, 92 patients, 44 males (47.8%) and 48 females
(52.2%) with a mean age of 60.4 years (range 15-86) were
studied. Most of the tumors were located on the trunk
(57.6%), the remaining on the limbs. The most common
dermoscopic patterns were multicomponent in 51 (55.4%) and reticular in 27 (29.3%). Dermoscopic
erosions/ulceration was observed in 18 tumors (19.6%).

### Reflectance Confocal Microscopy Attributes

Table 1 summarizes the dermoscopic and confocal features
evaluated. According to the melanoma RCM classification [13],

<table>
<thead>
<tr>
<th>Dermoscopic Features</th>
<th>Primary Melanomas (N= 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global pattern</td>
<td></td>
</tr>
<tr>
<td>Reticular</td>
<td>27 (29.3%)</td>
</tr>
<tr>
<td>Multicomponent</td>
<td>51 (55.4%)</td>
</tr>
<tr>
<td>Unspecific</td>
<td>12 (13.0%)</td>
</tr>
<tr>
<td>Globular</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Pigmented Network</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>20 (21.7%)</td>
</tr>
<tr>
<td>Typical</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>66 (71.7%)</td>
</tr>
<tr>
<td>Globules</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>27 (29.3%)</td>
</tr>
<tr>
<td>Typical</td>
<td>7 (7.6%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>58 (63.0%)</td>
</tr>
<tr>
<td>Streaks</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>35 (38.0%)</td>
</tr>
<tr>
<td>Typical</td>
<td>16 (17.4%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>41 (44.6%)</td>
</tr>
<tr>
<td>Structureless areas</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>70 (76%)</td>
</tr>
<tr>
<td>Present</td>
<td>22 (24%)</td>
</tr>
<tr>
<td>Blue-white veil</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>61 (66.3%)</td>
</tr>
<tr>
<td>Present</td>
<td>31 (33.7%)</td>
</tr>
<tr>
<td>Regression</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>49 (53.3%)</td>
</tr>
<tr>
<td>Present</td>
<td>43 (46.7%)</td>
</tr>
<tr>
<td>Milky-red areas</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>60 (65.2%)</td>
</tr>
<tr>
<td>Present</td>
<td>32 (34.8%)</td>
</tr>
<tr>
<td>Shiny-white streaks</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>37 (40.2%)</td>
</tr>
<tr>
<td>Present</td>
<td>55 (59.2%)</td>
</tr>
<tr>
<td>Rosettes</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>75 (81.5%)</td>
</tr>
<tr>
<td>Present</td>
<td>17 (18.5%)</td>
</tr>
<tr>
<td>Vessels</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>48 (52.2%)</td>
</tr>
<tr>
<td>Present</td>
<td>44 (47.8%)</td>
</tr>
<tr>
<td>Dotted</td>
<td>25 (27.2%)</td>
</tr>
<tr>
<td>Hairpin</td>
<td>8 (8.70%)</td>
</tr>
<tr>
<td>Polymorphic</td>
<td>27 (29.3%)</td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 (Continued)
The Barcelona algorithm score was equal to or higher than 0 in 84 out of 92 cases (91.3%), which is highly suggestive of melanoma; the remaining 8 (8.7%) achieved a score of -1, which means it could be melanoma [9].

### Histological Characterization

The most common histological subtype observed was superficial spreading melanoma (SSMM) in 52 (56.6%) of the cases, followed by in situ melanomas in 28 lesions (30.4%), lentigo maligna melanoma (LMM) in 6 (6.5%), nodular (NM) in 5 (5.4%) and one spitzoid melanoma (1.1%). Only 6.5% of melanomas presented histological ulceration. According to tumor infiltrating lymphocytes (TILs), 58 cases (63%) were

<table>
<thead>
<tr>
<th>Dermoscopic Features</th>
<th>Primary Melanomas (N = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>74 (80.4%)</td>
</tr>
<tr>
<td>Present</td>
<td>18 (19.6%)</td>
</tr>
<tr>
<td>Atypical Blotches</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>63 (68.5%)</td>
</tr>
<tr>
<td>Present</td>
<td>29 (31.5%)</td>
</tr>
<tr>
<td>Negative network</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>74 (80.4%)</td>
</tr>
<tr>
<td>Present</td>
<td>18 (19.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confocal Characteristics</th>
<th>Primary Melanomas (N = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal Cobblestone</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>38 (41.3%)</td>
</tr>
<tr>
<td>Typical</td>
<td>21 (22.8%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>33 (35.9%)</td>
</tr>
<tr>
<td>Epidermal Honeycomb</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>7 (7.6%)</td>
</tr>
<tr>
<td>Typical</td>
<td>39 (24.4%)</td>
</tr>
<tr>
<td>Atypical</td>
<td>46 (50.0%)</td>
</tr>
<tr>
<td>Epidermal Disarranged</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>34 (37.0%)</td>
</tr>
<tr>
<td>Present</td>
<td>58 (63.0%)</td>
</tr>
<tr>
<td>Large pagetoid round cells</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>14 (15.3%)</td>
</tr>
<tr>
<td>Present</td>
<td>78 (84.7%)</td>
</tr>
<tr>
<td>Large pagetoid dendritic cells</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>31 (33.7%)</td>
</tr>
<tr>
<td>Present</td>
<td>61 (66.3%)</td>
</tr>
<tr>
<td>Atypical pagetoid pleomorphic cells</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>84 (91.3%)</td>
</tr>
<tr>
<td>Present</td>
<td>8 (10.2%)</td>
</tr>
<tr>
<td>Pagetoid star-shaped cells</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>90 (97.8%)</td>
</tr>
<tr>
<td>Present</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Mainly edged papilla</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>53 (57.6%)</td>
</tr>
<tr>
<td>Present</td>
<td>39 (42.4%)</td>
</tr>
<tr>
<td>Typical cells at the basal</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>77 (83.7%)</td>
</tr>
<tr>
<td>Present</td>
<td>15 (16.3%)</td>
</tr>
<tr>
<td>Atypical Basal Round cells</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>20 (21.7%)</td>
</tr>
<tr>
<td>Present</td>
<td>72 (78.3%)</td>
</tr>
</tbody>
</table>

| Nucleated dermal cells   |                             |
| Absent                   | 56 (60.9%)                  |
| Present                  | 36 (39.1%)                  |
| Dermal Nests             |                             |
| Absent                   | 39 (42.4%)                  |
| Present                  | 53 (55.6%)                  |
| Dense                    | 54 (58.7%)                  |
| Sparse cell              | 1 (1.1%)                    |
| Cerebriform              | 5 (5.4%)                    |
| Inflammatory cells in dermis |                        |
| Plump cells              | 40 (43.5%)                  |
| Bright particles         | 88 (95.7%)                  |
| Collagen bundles         |                             |
| Visible                  | 59 (64.1%)                  |
| Non visible              | 33 (35.9%)                  |
| Dermal vessels           |                             |
| Absent                   | 69 (75.0%)                  |
| Present                  | 23 (25.0%)                  |
| Horizontal               | 11 (12.0%)                  |
| Coiled                   | 2 (2.2%)                    |
| Thin / Thick             | 3 (3.3%) / 20 (21.7%)       |

Table 1. Dermoscopic and reflectance confocal features. (Continued)
considered non-brisk, while 28 (30.4%) were considered brisk; in 6 (6.5%), TILs were absent. The predominant cytology was epithelioid (ovoid) in 49 (53.3%) cases. Growth pattern was classified into marked scattered or pagetoid in 25 (27.2%) cases, moderate in 22 (23.9%) and mild in 38 (41.3%), while nesting pattern was considered marked in 28 (30.4%), moderate in 11 (12%) and mild in 30 (32.6%). Cytoplasmic pigmentation was absent in 11 cases (12%), faint in 26 (28.3%), moderate in 35 (38%), high in 13 (14.1%), and very high in 7 (7.6%).

Some degree of solar elastosis was present in 70 patients (80.4%). Only 2 patients presented vascular invasion and 1 neural invasion. Regression was classified as marked (> 50% of surface) in 20 (21.7%), partial (< 50%) in 27 (29.3%), focal in 20 (21.7%) and absent in 25 (27.2%) cases. Among the invasive cases (N = 64) the mean Breslow index was 1.43 mm (SD 1.6). The mean mitotic rate was 1.25/mm² (SD 2.0): in 29 invasive cases (45.3%) less than 1 mitosis/mm², and 10 cases (15.6%) between 1 and 3 mitosis/mm². The remaining 12 cases (18.7%) showed a high mitotic index (4 or more mitosis/mm²). Table 2 summarizes the histopathology in detail.

**Association of in Vivo Findings with Histological Prognostic Markers (Table 3)**

**Dermoscopic Correlations**

As regards the global dermoscopic pattern, a multicomponent pattern was associated with higher nesting growth on histology (P = 0.05) while a reticular pattern was protective against nesting on histology (P = 0.001).

The presence of a pigment network was related to a lower Breslow index and lower mitotic rate (both P = 0.002), while the presence of blotches, structureless pigmentation, visible vessels and blue white veil were related to a higher Breslow index and mitotic rate (P = 0.05, p < 0.01, P < 0.01 and P < 0.01 respectively).

Multivariate analysis demonstrated that a dermoscopic pigment network was related to a lower Breslow index and a lower mitotic rate (both P = 0.002), while the presence of atypical blotches was related to a higher Breslow index and mitotic rate (P = 0.05, P < 0.01).

**Confocal Correlations**

The presence of typical epidermal cobblestone and honeycomb patterns was more likely to be associated with in-situ melanos (51.7% and 53.6% of in situ cases, P = 0.04), and as expected, the presence of mainly edged papillae as well (48.7% of in situ versus 20.1% of invasive cases, P = 0.005).

The observation of atypical epidermal cobblestone was related to lentigo maligna subtype (LMM), seen in 50% of cases, in contrast to 34.8% of non-LMM cases (P = 0.04).

---

**Table 2. Histopathological characterization**

<table>
<thead>
<tr>
<th>Histological features</th>
<th>Primary melanomas (n:92)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological Type</strong></td>
<td></td>
</tr>
<tr>
<td>In situ</td>
<td>28 (30.4%)</td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>52 (56.7%)</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Nodular</td>
<td>5 (5.4%)</td>
</tr>
<tr>
<td>Spitzoid</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td><strong>Clark Level</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10 (10.9%)</td>
</tr>
<tr>
<td>III</td>
<td>22 (23.9%)</td>
</tr>
<tr>
<td>IV</td>
<td>30 (32.6%)</td>
</tr>
<tr>
<td><strong>Mitotic Rate</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1/mm²</td>
<td>29 (45.3%)</td>
</tr>
<tr>
<td>1-3/mm²</td>
<td>10 (15.6%)</td>
</tr>
<tr>
<td>&gt; 4/mm²</td>
<td>12 (18.7%)</td>
</tr>
<tr>
<td><strong>Pagetoid infiltration grade / Scattered cells</strong></td>
<td></td>
</tr>
<tr>
<td>0 none</td>
<td>7 (7.6%)</td>
</tr>
<tr>
<td>1 mild</td>
<td>38 (41.3%)</td>
</tr>
<tr>
<td>2 moderate</td>
<td>22 (23.9%)</td>
</tr>
<tr>
<td>3 marked</td>
<td>25 (27.2%)</td>
</tr>
<tr>
<td><strong>Nesting grade</strong></td>
<td></td>
</tr>
<tr>
<td>0 none</td>
<td>23 (25%)</td>
</tr>
<tr>
<td>1 mild</td>
<td>30 (32.6%)</td>
</tr>
<tr>
<td>2 moderate</td>
<td>11 (12.0)</td>
</tr>
<tr>
<td>3 marked</td>
<td>28 (30.4%)</td>
</tr>
<tr>
<td><strong>Cytoplasmatic Pigmentation</strong></td>
<td></td>
</tr>
<tr>
<td>Faint</td>
<td>26 (28.3%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>35 (38.0%)</td>
</tr>
<tr>
<td>High</td>
<td>13 (14.1%)</td>
</tr>
<tr>
<td>Very High</td>
<td>7 (7.6%)</td>
</tr>
<tr>
<td><strong>Cytomorphology</strong></td>
<td></td>
</tr>
<tr>
<td>Round</td>
<td>29 (31.5%)</td>
</tr>
<tr>
<td>Ovoid</td>
<td>49 (53.3%)</td>
</tr>
<tr>
<td>Elongated</td>
<td>10 (10.9%)</td>
</tr>
<tr>
<td>Spindled</td>
<td>4 (4.3%)</td>
</tr>
<tr>
<td><strong>Elastosis</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>28 (30.4%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>29 (31.5%)</td>
</tr>
<tr>
<td>Marked</td>
<td>17 (18.5%)</td>
</tr>
<tr>
<td><strong>Ulceration</strong></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>TIL’s Brisk</td>
<td></td>
</tr>
<tr>
<td>Non-Brisk</td>
<td>58 (63.0%)</td>
</tr>
<tr>
<td>Brisk</td>
<td>34 (37.0%)</td>
</tr>
<tr>
<td><strong>Type of growth</strong></td>
<td></td>
</tr>
<tr>
<td>Vertical</td>
<td>62 (67.4%)</td>
</tr>
<tr>
<td>Radial</td>
<td>30 (32.6%)</td>
</tr>
<tr>
<td><strong>Regression</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>20 (21.7%)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>27 (29.3%)</td>
</tr>
<tr>
<td>Focal</td>
<td>20 (21.7%)</td>
</tr>
<tr>
<td><strong>Vascular Invasion</strong></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Neural Invasion</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>
Table 3. Dermoscopic and confocal features with prognostic value (P < 0.05).

<table>
<thead>
<tr>
<th>Higher Breslow:</th>
<th>Mitotic Rate:</th>
<th>Lower Breslow:</th>
<th>Mitotic Rate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermoscopic Criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical blotches</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structureless pigmentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visible vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCM Criteria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bright particles and plump cells in dermis</td>
<td>Edged papillae and typical epidermis*</td>
<td>Typical cells in basal layer</td>
<td></td>
</tr>
<tr>
<td>Dermal nests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical nucleated cells in dermis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Existence of typical honeycomb and cobblestone patterns in epidermis, and edged papillae were associated with in situ melanomas.

Figure 1. Dermoscopic and Confocal findings in primary melanoma. (A) Clinical appearance of pigmented asymmetric lesion on the leg. (B) Dermoscopic presence of asymmetric polychromic lesion, showing negative network (white square), blue-white veil, atypical vessels (red square), ulceration and structureless pigmented areas. (C) Reflectance Confocal Microscopy (RCM) imaging (800 microns x 800 microns) at dermoepidermal junction (DEJ) and superficial dermis showing cerebriform nests with amorphous pleomorphic cells. Non edged papillae and atypical cells were visible at DEJ. (D) RCM imaging (1 mm x 1 mm) at superficial dermis demonstrated multiple atypical high caliber vessels (red squares).

Atypical honeycomb was more frequently found in superficial spreading melanomas (SSMM) - seen in 65.2% while only in 37.5% of non-SSMM cases (P = 0.03). The presence of large atypical pagetoid cells and the dendritic shape of pagetoid cells were both more frequent in SSMM (60.7%, P = 0.01 and 59%, P = 0.05; respectively). Importantly, confocal observation of dermal nests showed a mean increase of 1.6 mitosis over the mean mitotic rate.
(P = 0.006) and the presence of bright particles and plump cells (that is, diffuse inflammatory infiltrate in the superficial dermis) was associated with a mean increase of 0.6 mm in the Breslow index (P = 0.04) and a higher mitotic rate (P = 0.04). The presence of atypical nucleated cells within dermal papillae was strongly associated with a higher mitotic rate (P = 0.003). On the other hand, the presence of typical basal cells was related to a lower mitotic rate (P = 0.002).

As regards the confocal patterns, a dendritic confocal pattern was significantly associated with brisk tumour infiltrating lymphocytes (TILs) (29.4%, P = 0.021). The dendritic subtype tends to appear in tumors showing more histological regression, but the association was not significant, (P = 0.38). No other significant associations were found regarding the 4 melanoma confocal subtypes. Histological ulceration was not associated with any specific confocal pattern: it was observed in 2.4% dendritic confocal patterns (P = 0.16) and in 11% combined confocal patterns (P = 0.47).

Conclusions

The present study on 92 primary melanomas allowed the identification of in vivo features related to the main histological prognostic factors in localized melanoma. The in vivo predictors of high mitotic rate and tumor thickness are 1) dermoscopically: absence of pigment network and the presence of structureless pigmentation and vessels, and 2) confocal dermal presence of: diffuse inflammatory infiltrate, atypical nucleated cells and nests (related only to a higher mitotic rate).

Dermoscopy has previously been demonstrated to predict histologic features such as regression phenomena or melanoma depth [18-23]. Further, the presence of a brown atypical pigmented network has been associated with melanomas showing no mitoses [4]. In accordance with the literature, the present study validates the observation of a dermoscopic pigmented network as related to early melanomas (that is, with both lower Breslow index and mitotic rate). Additionally, we found that visualization of atypical vessels, blotches or structureless pigmentation are related to higher thickness.

In contrast to what we expected, the presence of dermoscopic ulceration and blue-white veil were not significantly associated with higher invasiveness or mitotic rate as reported by Deinlein et al [5]. Interestingly, in our series, there was a notable discrepancy between dermoscopic ulceration (present...
in almost 20% of cases) and histopathologic ulceration (less than 7% were ulcerated in the definite report).

Interestingly, dermoscopy of primary melanoma has also been demonstrated as useful in predicting sentinel lymph node biopsy status [6]. There is a dermoscopic algorithm, which can achieve a sensitivity of 96.3% and a specificity of 52.1% (P < 0.001) for positive sentinel lymph node prediction.

On the other hand, molecular studies support the view that melanoma comprises distinct types of tumors and suggest that specific morphological features may help predict its clinical behavior. In line with this, and given some dermoscopic attributes of melanoma, such as features of regression and vascularity, were strongly linked to the overall amount of genomic damage [24].

In the present study, with the addition of confocal pre-surgical characterization, we demonstrated that a higher mitotic index is expected when dermal nests and atypical nucleated cells are found. In addition, a higher mitotic index and Breslow depth can be predicted when diffuse inflammatory infiltrate is observed in the superficial dermis.

As also described by Grazziantin et al in the setting of multiple primary and familial melanomas in our center, we could validate the confocal classification of sporadic melanomas into the 4 confocal types [19]. In our series the predominant confocal pattern was the dendritic cells subtype (44.6%) in contrast to the Pellacani et al cohort, which found a similar value for the combined type (47%). In our series the combined type was seen only in 9.8% of the 92 cases. However, this is in line with Grazziantin et al who found only 2 combined cases (4%) in a multiple and familial melanoma series of 57 cases from our center. This difference could be explained in part due to 1) the location of the present cohort of tumors (only trunk and limbs were included) and 2) in an attempt to avoid a large number of non-classifiable melanomas, we tried to classify all melanomas according to the predominant cell type present in more than 50% of the lesion, as done by Grazziantin et al [25]. On the other hand, Pellacani et al hypothesized that combined type could be a more advanced stage of other types, although in our series this could not be demonstrated, despite the fact that our mean Breslow (1.43 mm, SD 1.6) was higher than in their series (mean 0.79 mm, SD 0.99). Interestingly, melanoma RCM subtypes have been correlated with different profile expression markers, that could be suggestive of progression and an increase in aggressiveness, depending on RCM morphologies [26].

The main limitations of the present study include that it is a retrospective single-centre study, with a limited sample where only melanomas located on trunk and limbs were included. Further studies which combine different imaging techniques will allow better in vivo characterization of skin tumors, such as the complementation of RCM with optical coherence tomography, which has a deeper reach and a dynamic mode of vascular examination [29,30].

The relevance of this study lies in the identification of in vivo predictors of melanoma thickness and high mitotic rate by dermoscopically identifying the absence of pigment network and the presence of structureless pigmentation and vessels, and on RCM, the presence of nests and diffuse inflammatory infiltrate in the dermis. A more accurate prediction of prognosis prior to excision of a primary tumor would optimize the first approach to melanoma patients in terms of accurate indications for radiologic staging tests and for surgery. This preliminary study lays out a new approach to further characterization of early junctional phenomena, crucial for melanoma progression such as the study of TILs and environmental interaction between melanoma cells and host stroma.

References


Dermoscopy of Linear Basal Cell Carcinomas, a Potential Mimicker of Linear Lesions: a Descriptive Case-series

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Key words: dermoscopy, dermatoscopy, basal cell carcinoma, skin cancer, linear


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ABSTRACT

Introduction: Among the various widely recognized basal cell carcinoma (BCC) clinical patterns, linear basal cell carcinoma (LBCC) is an uncommon morphologic variant of BCC.

Objectives: Describe the clinical and dermoscopic characteristics of LBCC.

Methods: Retrospective study including LBCC cases from 5 dermatology centers in North and South America. Biopsy-proven primary BCCs, that presented with at least 3:1 length:width ratio on physical examination, irrespective of tumor subtype or location, were included. Clinical and dermoscopic analysis were performed by 2 experts in dermoscopy.

Results: Eighteen cases of LBCC met our inclusion criteria and were included in the study. Median age at diagnosis was 86.0 years, 10 patients (58.8%) were males. Regarding anatomic location, 11/18
Introduction

Basal cell carcinoma (BCC) is the most common skin cancer worldwide [1]. Several BCC classifications have been proposed based on its clinical and histopathological characteristics [2]. Among the various widely recognized BCC clinical patterns, linear basal cell carcinoma (LBCC) is an uncommon morphologic variant of BCC which was described by Lewis et al [3]. It was defined as ‘a lesion that extends preferentially in one direction, resulting in a tumor or plaque with a length much greater than its width greater than 3:1 ratio’ [3-5]. Due to this linear morphology, LBCC can clinically mimic scars, scratches, striae, or tattoos, among other diagnoses. Although there is an extended literature with regards to the dermoscopic findings of BCC in general [6-9], little is known regarding the structures and patterns seen in LBCC under dermoscopy. Additionally, LBCC clinical features have been scarcely described.

Objectives

We sought to evaluate and describe the dermoscopic appearance and clinical characteristics of LBCC.

Methods

This retrospective observational study was approved by the IRB of Pontificia Universidad Católica de Chile (#201127004). We examined all cases of LBCCs between January 2016 to January 2021 from 6 dermatologic centers in 3 countries (Santiago, Chile; Sao Paulo, Brazil; Miami, FL, and New York, NY). A search was performed using clinical images of diagnosed BCCs. Eligibility criteria were based on clinical (not histopathological) features of BCC. Biopsy-proven primary BCCs, that presented with at least 3:1 length:width ratio on physical examination, irrespective of tumor subtype or location, were included. Recurrent BCCs were excluded, as they may present with a ‘false-positive’ linear appearance due to the nature of linear closures.

Patients demographics (age, gender) and subsequent treatment were recorded and maintained in a deidentified database. Clinical and dermoscopic images were obtained with 2 different devices depending on the center: A digital camera coupled with a digital dermatoscope (VEOS DS3, Canfield INC) and/or a Samsung Galaxy S5 coupled with a Dermlite DL3 dermatoscope (3Gen). Clinical images evaluated pigmentation status (yes/no) and whether tumors followed skin tension lines according to Newell et al [10]. Dermoscopic analyses were performed by 2 investigators (C.N.D. and A.A-A) based on the latest dermoscopic consensus by Kittler et al [11], and the most updated BCC criteria [12]. Images were evaluated in both polarized and non-polarized mode. When there was disagreement in dermoscopic interpretation, a third investigator served as a referee (M.A.M.).

Statistical Analysis

Data was analyzed using SPSS 23.0 (SPSS, Armonk). Measures of central tendency were calculated. Unless otherwise noted, all values are expressed as mean and standard deviation (SD).

Results

Eighteen cases of LBCC on 17 patients met our inclusion criteria and were included in the study; 1 patient contributed with 2 lesions. Median age at diagnosis was 86.0 years (SD 7.6; range 67 – 91 years), 10 patients (58.8%) were males; 72.2% (N = 13) were Hispanic/Latino and 27.8% (N = 5) were Caucasians.

In all, 11/18 (61.1%) cases were nodular, 5/18 (27.7%) cases were superficial, 1 case was morphea-form (5.5%), one case was infiltrative (5.5%). Regarding anatomical location, 11/18 (61.1%) were located on the head and neck, 5/18 (27.7%) cases were found on the trunk, and 2 on lower extremities (11.1%). When evaluating skin tension lines, 15/18 (83.3%) followed these lines. All tumors were submitted to pathological analysis with the clinical/dermoscopic diagnosis of BCC. Regarding treatment, 10/18 (55.5%) were treated with simple excision, 6/18 cases (33.3%) with Mohs micrographic surgery, and 1 case (5.5%) with electrodessication and curettage. One case was lost to follow-up.

Dermoscopic Analysis

Under dermoscopy, 15/18 (83.3%) of LBCC were dermoscopically pigmented and all had absence of reticular network. All tumors displayed at least one of the BCC-specific
dermoscopic criteria (Table 1) [12]: blue-gray globules (72.2%), in-focus dots (66.6%), short-fine telangiectasia (55.5%), leaf-like areas (61.1%), milky-red background (38.8%), ovoid nests (38.8%), ulceration/erosions (44.4%), shiny white blotches and strands (33.3%), arborizing vessels (22.2%), concentric structures (16.6%), and spoke-wheel structures (5.6%) (Figures 1-4).

Conclusions

In this retrospective study including 18 LBCC, we described the dermoscopic features of LBCC. Dermoscopy might be a useful tool for the diagnosis of this uncommon morphological subtype of BCC, as it presented with classic dermoscopic BCC criteria. No specific or novel dermoscopic findings appear to be associated with LBCC. The most common histopathologic subtype corresponded to the nodular subtype. Despite the broad clinical differential diagnosis of linear lesions (i.e. scars, scratches, striae, tattoos, among others), dermoscopy might be of aid in the diagnosis of LBCC, as the presence of at least one of the BCC-specific features described elsewhere in dermoscopy was seen in all our cases [6,12]. However, additional studies that include other linear lesions as controls are needed to confirm our results.

The most common location in our series was the head and neck. Some studies have shown the lower eyelid as the most frequent anatomic location [13] which was not confirmed by the present larger, multicentric study including 18 cases. Based on our study findings, LBCC can appear in any anatomical location. To the best of our knowledge, this is the largest study examining the clinical and dermoscopic presentation of LBCCs from diverse clinical settings [5-14].

An interesting finding of our series was that dermoscopically pigmented variants comprised >80% of LBCC (Figure

Table 1. Dermoscopic features seen in the 18 cases of linear basal cell carcinoma (in alphabetical order).

<table>
<thead>
<tr>
<th>Dermoscopic feature</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of pigment network</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Arborizing telangiectasia</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Blue-grey globules</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Concentric structures</td>
<td>3 (16.6)</td>
</tr>
<tr>
<td>In-focus dots</td>
<td>12 (66.6)</td>
</tr>
<tr>
<td>Leaf-like structures</td>
<td>11 (61.1)</td>
</tr>
<tr>
<td>Milky-red background</td>
<td>7 (38.8)</td>
</tr>
<tr>
<td>Ovoid nests</td>
<td>7 (38.8)</td>
</tr>
<tr>
<td>Shiny white blotches and strands</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Short-fine telangiectasia</td>
<td>10 (55.5)</td>
</tr>
<tr>
<td>Spoke-wheel like areas</td>
<td>1 (5.5)</td>
</tr>
<tr>
<td>Ulceration/erosion</td>
<td>8 (44.4)</td>
</tr>
</tbody>
</table>

Figure 1. Linear Basal Cell Carcinoma, pigmented. (A) Clinical photograph showing a linear pigmented plaque on neck following Langer lines on the clavicle. (B) Dermoscopic features showing blue-grey globules, ulceration, and leaf-like structures (polarized light, original magnification 10X). (C) Clinical photograph showing a linear, inconspicuous, pigmented plaque on chest following Langer lines. (D) Dermoscopic features showing leaf-like structures and in-focus dots (polarized light, original magnification 10X).
Figure 2. Linear basal cell carcinomas, pigmented. (A) Clinical photograph showing a linear black ulcerated tumor on the lateral neck following Langer lines. (B) Dermoscopic features blue-grey globules, leaf-like structures, and shiny white blotches and strands (polarized light, original magnification 10X). (C) Clinical photograph showing a linear pigmented plaque on the anterior leg following Langer lines. (D) Dermoscopic features showing blue-grey globules, leaf-like structures, in-focus dots, ulceration, and shiny white blotches and strands (polarized light, original magnification 10X).

Figure 3. Linear basal cell carcinoma, non-pigmented. (A) Clinical photograph showing 2 linear erythematous plaques on the neck following Langer lines. (B) Dermoscopic features showing short-fine telangiectasia, ulcerations, and shiny white blotches and strands (polarized light, original magnification 10X). (C) Clinical photograph showing a linear, inconspicuous pink plaque (demarcated by blue pen) on the neck following Langer lines. (D) Dermoscopic features showing arborizing vessels and shiny white blotches and strands (polarized light, original magnification 10X).
microscopy or optical coherence tomography might help to elucidate in vivo the tumor and stroma interaction \[17,18\].

The main limitations of our study are its retrospective nature, the lack of a control group, cases being non-consecutive subject to selection and recall bias, and its small sample size. Further, larger studies are needed to confirm our findings. Dermoscopy might be useful in the differentiation of LBCC from other diagnoses presenting as linear lesions such as scars, scratches/erosions, and tattoos, among others. Some of these lesions can be confused by naked eye examination alone. Additional case-control studies are needed to confirm our findings. The dermoscopic features seen in LBCC are similar to those commonly found in classic BCCs.

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References


Investigation on Utility of Some Novel Terpenes on Transungual Delivery of Terbinafine for the Management of Onychomycosis

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ABSTRACT

Introduction: Onychomycosis is a fungal disorder of the nail which afflicts 5% of the population worldwide. The disease is strenuous to cure as it is chronic, hard to eliminate and tends to recur. Topical therapy is at the forefront for the treatment of many disorders of nail. However, the success rate of topical therapy has been halted owing to the poor permeation of topical therapeutics across densely keratinized nail barrier. Therefore, ungual drug permeation must be improved for an effective topical therapy. An approach to achieve this goal would be the use of terpenes from natural sources as potential penetration enhancers.

Objective: This study is aimed to explore the effectiveness of some novel terpenes as potential penetration enhancers on transungual delivery of terbinafine.

Methods: Ex-vivo permeation studies were performed by sopping the nail clippings of healthy human volunteers in control and working solutions containing terbinafine (5mg/ml) per se and terbinafine (5mg/ml) with 6% of each terpenes including lavandulol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool respectively for 48 hours. The terbinafine concentration in nail samples was determined using a HPLC (High Performance Liquid Chromatography method.

Results: Statistical analysis showed that studied terpenes increase transungual penetration of terbinafine in the following order: linalool > rose oxide > 3-methyl-2-butene-1-ol > safranal > limonene > lavandulol acetate. Accordingly, linalool was found to be the most effective penetration enhancer for the transungual delivery of terbinafine.

Conclusions: It is concluded that linalool can be used as safe and potential penetration enhancer for enhancing the transungual delivery of terbinafine for onychomycosis.
Introduction

Onychomycosis is the most prevalent fungal disorder of the nails attributable to yeasts (Candida albicans and other candida species), non-dermatophyte molds (Scytalidium hyalinum, Scopulariopsis brevicaulis, Acremonium sp., Aspergillus Sp., S.dimitatum), and dermatophytes (Trichophyton rubrum, T. krajdenii, T. mentagrophytes, Epidermophyton floccosum) [1]. Due to this infection, the patients experience a prodrome of nail plate thickening, onycholysis, and nail discoloration. The afflicted patients experience paresthesia, local pain, and reduced quality of life. The abnormal appearance of the nails may plague the daily activities and stigmatize social life of affected persons [2]. Onychomycosis progression increases with simultaneous inhabitation of other conditions like HIV, poor peripheral circulation, diabetes, and immunosuppression [1].

The onychomycosis treatment always remains challenging due to the thick impermeable property of the nail and profound infection [3]. However, oral treatment therapy remains the priority for the affected patients due to the accessibility and efficacy of oral therapeutics [2]. The oral treatment includes anti-fungal drugs from allylamine and azole classes. The azole class includes ketoconazole, fluconazole and itraconazole and the allylamine class includes terbinfine wherein itraconazole and terbinfine are US FDA approved medications for onychomycosis treatment [4-6]. Terbinfine excels over itraconazole due to higher cure rate and fewer drug interactions. However, their effectiveness is defined/constrained due to their limited availability at the site of action, which further increases treatment duration, treatment cost, side effects like cardiac disturbances and hepatic toxicity, and drug interactions. The topical treatment provides an alternative approach to evade the drawbacks associated with oral medicines and improves the adherence and localized effect [7-12].

The topical treatments approved by the FDA for effective treatment of onychomycosis include tavaborole 5% solution, ciclopirox 8% nail lacquer, and efinaconazole 10% solution [13-14]. However, their effectiveness is limited due to the minimal permeability of the drug across the nail plate. The nail impermeability can be accredited to the highly stable hydrogen bonds and disulfide linkages in the keratin network. Moreover, globular proteins and keratin fibres make a complex structure that makes the nail plate the most challenging biological barrier [3]. Therefore, extensive research has been focused on altering the nail plate barrier by employing various approaches, which include physical methods, mechanical methods, chemical treatments, and penetration enhancers; wherein one of the most commonly used approaches is the use of penetration enhancers, which act by disrupting the keratinized structure of nail plate thereby increasing the diffusion gradient and penetration capacity of the active through the nail plate [15-18].

Researches from past decades have shown that chemical penetration enhancers yield higher permeation rates than other approaches for effective transungual delivery, but irritancy at the site of application always remains a challenge [19,20]. Therefore, research has been oriented towards finding safe and effective penetration enhancers from natural sources. Terpenes acquired from natural sources have emerged as promising candidates and are considered as clinically acceptable penetration enhancers. In addition, many terpenes appear in the list of generally recognized as safe (GRAS) agents published by the USFDA. Terpenes are used for permeation enhancements of both lipophilic and hydrophilic drugs. Their activity depends on their chemical structure and physicochemical properties such as degree of unsaturation, boiling point, size and chirality, the energy of vaporization, and lipophilicity [21].

In the present study, we chose terbinafine, an allylamine fungicidal drug that acts by inhibiting squalene epoxidase in the ergosterol biosynthesis pathway and shows higher efficacy against dermatophytes and many non-dermatophytes [22]. Topical therapy can eminently treat onychomycosis. The route is highly advantageous attributable to its localised effect and minimal adverse effect profile. However, its potential is hampered by the rigid keratinous structure of the nail plate which is hard to breach [23].

Objectives

Therefore, our research has been centered on improvement of transungual delivery of terbinafine with the assistance of natural permeation enhancers ie terpenes viz. lavandulol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool. The salient features of the studied terpenes have been highlighted in Table 1.

Methods

Terbinafine was purchased from Virupaksha Organics Limited. Lavandulol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool were purchased from Sigma-Aldrich. Absolute ethanol, methanol, hydrochloric acid, sodium hydroxide, propylene glycol, Tween 80, and HPLC grade methanol were purchased from S.D. Fine Chemicals. All chemicals were of Analytical Reagent grade.

Liquid Chromatographic Conditions

HPLC Quaternary System consisting of lichrospher C18 reverse-phase column of 2.5 x 4.6 mm with particle size of 5 µm was used for performing HPLC analysis. All analyses were carried out under isocratic conditions at a flow
rate of 1ml/min using mobile phase methanol: acetonitrile: 0.2% triethylamine (55:35:10, %v/v) with U.V. detection at 280 nm [24].

**Preparation of Stock and Working Solutions**

In propylene glycol: tween 80: ethanol: dimethyl sulfoxide (30: 3: 62: 5), the stock solution of terbinafine (25 mg/ml) was prepared and stored at -20°C. By diluting the stock solution in water: ethanol (50:50, v/v) five times, terpene-free working solution (control) was prepared. The concentration was selected based on the method sensitivity used in the experiment and the terbinafine solubility. Further, 6 working solutions were prepared, each containing 5 mg/ml of terbinafine stock solution and 6% of terpenes (solution B, C, D, E, F, and G labelled for lavandulol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool respectively). To assess the optimal effect of terpenes on transungual delivery of terbinafine, terpenes concentration was chosen to be more than 4.7%, which emulated the highest concentration of terpene in market formulation viz. Vicks Vaporub® (camphor, 4.7%). The prepared solutions were subjected to nail penetration studies [25].

**Ex-vivo Nail Penetration Studies**

Healthy adult volunteers (5 women, 5 men, 18-50-years-old, N = 10) who were not on any prescribed drug were chosen for sample collection. Nail samples were collected using nail clippers and scissors. After giving a brief description about the experiment, written consent was taken from all participating individuals. No ethical approval was needed since nails are waste materials and voluntarily donated by the participants. After collecting nail samples, each nail was cut into

<table>
<thead>
<tr>
<th>Name</th>
<th>Molecular Formula</th>
<th>Structure</th>
<th>Type</th>
<th>Log P</th>
<th>Boiling Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavandulol acetate</td>
<td>C_{12}H_{20}O_{2}</td>
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<tr>
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<td>Monoterpene</td>
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<td>71-73 °C</td>
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<td>Monoterpene</td>
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<td>175 °C</td>
</tr>
<tr>
<td>3-methyl-2-buten-1-ol or prenol</td>
<td>C_{5}H_{10}O</td>
<td><img src="image" alt="3-Methyl-2-Buten-1-Ol" /></td>
<td>Monoterpene</td>
<td>0.91</td>
<td>140 °C</td>
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<tr>
<td>Linalool</td>
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<td><img src="image" alt="Linalool" /></td>
<td>Monoterpene</td>
<td>2.7</td>
<td>198.5 °C</td>
</tr>
</tbody>
</table>
small pieces; 25 mg of nail sample was used for each experiment [25]. To remove the adhered dirt from the surface and prevent any interference in the study, 20 ml of water was added to the nail samples to digest for 20 minutes. Then, nail samples were washed with methanol three times and then air-dried. Further, the nail samples were stored at a room temperature in a sealed plastic bags till analysis.

Eight propylene tubes of 2 ml capacity were taken and eight aliquots (each 25 mg) of nail samples of each volunteer were transferred into it. One ml of a drug-free working solution was taken in the first tube as blank sample (solution A). To determine the effect of terpenes on the penetration of terbinafine across the nail samples, 1 ml each of blank solution A and working solutions B, C, D, E, F, and G was added to the remaining tubes and kept at room temperature for 48 hours. Further, nail samples were sonicated for 15 minutes with 10 ml methanol thrice to remove the adhered drug residue from the surface.

Further, the samples were transferred to the centrifuge tubes. Then, the tubes were incubated after addition of 1ml of 0.5 M NaOH for 12 hours to digest the samples. The samples were neutralized by adding 0.5 M HCl solution. The samples were then vortexed for 2 minutes and centrifuged at 6000 rpm for 20 minutes. The supernatant was collected and the concentration of terbinafine in 20 µl of each solution was determined by HPLC analysis.

Stability of Terbinafine in the Digestion Procedure
In propylene glycol: tween 80: ethanol: dimethyl sulfoxide (30: 3: 62: 5 v/v) vehicle, 1 mg/ml stock solution of terbinafine was prepared. The 100 µl/ml solution of terbinafine was prepared by diluting the stock solution 10 times in water: methanol (50:50, v/v). Further, two different solutions were prepared using this solution. First, an aqueous solution of 5 µl/ml of terbinafine was made by diluting the above solution 20 times, and 20 µL of the prepared aqueous solution was subjected into the column. Secondly, a 5 µl/ml solution was made in 0.5 M NaOH and incubated for 12 hours. After incubation, the solution was neutralized by adding 0.5 M HCl, centrifuged; and 20 µL of this solution was subjected for HPLC analysis. To determine the stability of terbinafine in the digestion procedure, the experiment was repeated three times to ascertain the stability of terbinafine in the digestion procedure by taking into consideration the dilution factor and the areas attained after injection of aqueous and basic solutions.

Preparation of the Calibrators
In 0.5 M NaOH, five calibrators of different concentrations of 5, 7.5, 10, 12.5, and 15 µg/ml were prepared from 1mg/ml stock solution of terbinafine. For HPLC analysis of calibrators, the aforementioned procedure was employed.

The concentration of terbinafine in nail samples was determined from the calibration curve plotted using the above five calibrators.

Statistical Analysis
The outcome result of the terbinafine extraction from the nail samples of the control solution (without terpene) was compared individually with the results acquired with each test solution (carrying 6% terpene) by statistical analysis. Shapiro-Wilk test was employed to determine the normal distribution of variables using SigmaPlot v 14.0 software. For comparing the quantitative variables with normally distributed and non-normally distributed quantitative variables, Paired t-test and Mann-Whitney U test were employed, respectively, and a P value < 0.05 was considered statistically significant.

Results
Sample Preparation and Drug Stability
To assess the transungual permeation of the drugs, the nail samples of the human volunteers were digested in various media [25]. Alkaline, acidic and methanolic digestion methods were used to hydrolyze the nail matrix. Various digestion procedures have been reported, including acid digestion by HCl (0.1 – 5.0 M), basic digestion by NaOH (1-10 M), digestion by nitric oxide (5% – 60%), their combination with methanol and hydrogen peroxide at a temperature between 25-60°C and digestion with benzyltrimethyl ammonium hydroxide. Stability of terbinafine was determined with the above methods (data not shown); eventually basic digestion by NaOH (0.5 M) for 16 hours at room temperature was found as the best approach to digest the nail samples. The recovery of terbinafine by applying this method was found to be 30.7%.

Ex-vivo Nail Penetration and Statistical Analysis
The experimental data from ex-vivo nail penetration studies and statistical analysis are presented in Table 2 and HPLC chromatograms of drug-free (blank), calibrator (standard terbinafine) and sample solution (terpene spiked) are shown in Figure 1.

The concentration of terbinafine in nail samples of control, lavandulol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool was found ranging from 3.094 to 3.445 µg/mg (3.280 ± 0.122), 3.372 to 3.548 µg/mg (3.486 ± 0.051), 3.419 to 3.774 µg/mg (3.601 ± 0.115), 4.469 to 4.682 µg/mg (4.554 ± 0.061), 3.502 to 3.605 µg/mg (3.551 ± 0.038), 4.386 to 4.538 µg/mg (4.463 ± 0.041) and 4.708 to 4.796 µg/mg (4.748 ± 0.028) respectively. After employing Mann-Whitney U test, the results showed a significant
and effective permeation enhancers from natural sources. In particular, terpenes have gained significant interest and are considered clinically acceptable permeation enhancers [21]. These promising candidates are considered effective and constitute a very safe class of permeation enhancers acquired from natural sources.

Furthermore, a good number of terpenes is incorporated in the list of generally recognized as safe (GRAS) classified by the US FDA [21]. The penetration enhancement ability of terpenes for hydrophobic and hydrophilic drugs are ascribed to their chemical structure in addition to the physicochemical properties, including size and chirality, degree of unsaturation, lipophilicity, the energy of vaporization, and boiling point [21].

In the past decades, several findings have shown that in vitro transungual studies are used to simulate and characterize the in vivo nail permeability. Permeation studies using Franz diffusion cells, measurement of nail swelling and drug uptake by nails after soaking nail clippings in drug solutions are often used. Though, in the recent works, it was found that keratin guards the analyte present in the nail matrix and hampers the availability of solvent and other reagents [18]. Hence, a digestion step was required to assess the terbinafine concentration in the nail before analysis. In the present study, effect of different terpenes was investigated on the transungual permeation of terbinafine and these were found to increase its permeation in following order: linalool > rose oxide > 3-methyl-2-butene-1-ol > safranal> limonene > lavandulol acetate. Thus, linalool was found to be the most effective penetration enhancer for the transungual delivery of terbinafine.

Conclusions

Topical therapy is at the forefront for the treatment of many disorders of nail and skin due to higher patient compliance and lesser side effects accompanied with systemic therapy. Howbeit, the nail disorders are frequently strenuous to cure and require long term therapy. The nail plate is an aggregate of highly dense keratinized tissue which in turn gives low permeability to the diffusing substances [26]. A number of approaches have been shown to be effective in enhancing transungual permeation such as mechanical methods (nail abrasion and nail avulsion), physical techniques (U.V light, carbon dioxide laser, iontophoresis, occlusion and hydration, sonophoresis, photodynamic therapy, electroporation and acid etching) or use of chemical penetration enhancers (keratolytic agents, water, keratinolytic enzymes, urea, mercaptans, sulfides and hydrogen peroxides) [26].

Literature and patent search divulged that chemical penetration enhancers excel over other strategies for the transungual delivery of drugs. Albeit the concentration required to achieve useful levels of permeation enhancements may cause irritancy at the site of application [19,20]. Hence, the investigations have been diverted towards searching safe

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Control group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>Group E</th>
<th>Group F</th>
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<td>4.682</td>
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<td>SD</td>
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<td>0.115</td>
<td>0.061</td>
<td>0.038</td>
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Normality test

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<td>P value</td>
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<td>0.382</td>
<td>0.921</td>
<td>0.517</td>
<td>0.665</td>
<td>0.381</td>
</tr>
</tbody>
</table>

A= terbinafine; B = terbinafine with lavandulol acetate; C = terbinafine with safranal; D = terbinafine with rose oxide; E = terbinafine with limonene; F = terbinafine with 3-methyl-2-butene-1-ol; G = terbinafine with linalool.

Difference between the control group and the lavandulol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool groups. The above results reveal that terpenes increase transungual penetration of terbinafine in the following order: linalool > rose oxide > 3-methyl-2-butene-1-ol > safranal> limonene > lavandulol acetate.

Table 2. Concentration of Terbinafine (µg mg⁻¹) Found in Nail Samples from Healthy Individuals and the Results from Statistical Analysis.
Figure 1. (A) HPLC chromatogram of blank. (B) HPLC chromatogram of standard terbinafine. (C) HPLC chromatogram of sample terbinafine.
The present study concludes that terpenes including lavenderol, safranal, rose oxide, limonene, 3-methyl-2-butene-1-ol, and linalool accentuate the transungual penetration of terbinafine and among these, linalool has been found to be the most effective penetration enhancer for the transungual delivery of terbinafine. By virtue of their enhancing effect, formulation of terbinafine with one or combination of these terpenes could be beneficial in topical dosage form development for treatment of onychomycosis.

References

Association Between Atopic Dermatitis and Major Cardiovascular Outcomes: a Two-Sample Mendelian Randomization Study

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Key words: atopic dermatitis, cardiovascular disease, Mendelian randomization


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ABSTRACT

Introduction: Atopic dermatitis (AD) has been linked to cardiovascular disease (CVD) in population-based studies, however, their causal relationship is still unclear.

Objectives: To evaluate the causal association of AD with risk of cardiovascular outcomes using a Mendelian randomization (MR) approach.

Methods: We extracted summary-level data for AD, stroke, heart failure, coronary artery disease (CAD), myocardial infarction, angina pectoris from published, nonoverlapping genome-wide association studies (GWAS). Inverse variance weighted (IVW) method was used as the primary analysis. Alternative methods, including weighted median, MR Egger, MR-Pleiotropy Residual Sum and Outlier, weighted mode, and leave-out analysis, were performed to examine potential pleiotropy.

Results: Thirteen SNPs (13,287 cases and 41,345 controls) were selected as instrumental variables (IVs). No associations of AD with risks of stroke (odds ratio [OR] = 1.03, 95% confidence interval [CI]: 0.97-1.09, P = 0.3630), heart failure (OR = 1.04, 95%CI: 0.99-1.09, P= 0.119), coronary artery disease (OR = 1.00, 95%CI: 0.96-1.05, P = 0.988), myocardial infarction (OR = 1.00, 95%CI: 1.00-1.00, P = 0.322), and angina pectoris (OR = 1.00, 95%CI: 1.00-1.00, P = 0.369) was found. No significant effect of pleiotropy was detected.

Conclusions: This MR study does not support a causal effect of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris.
Introduction

Atopic dermatitis (AD, atopic eczema, eczema) is a common chronic, inflammatory, relapsing, skin disease [1]. The prevalence of AD is 15 to 20% among children and 7% to 14% among adults [2,3]. It is characterized by eczematous lesions, varying degrees of pruritus, and a chronic or relapsing disease course [4]. AD broadly decreases health-related quality of life [5].

Recently, there has been a growing interest in the putative cardiovascular comorbidities of AD in population-based observational studies [6-11]. However, owing to the nature of being susceptible to potential confounders and reverse causation in observational study design [12], it remains unclear whether the elevated risk of CVD in patients with AD is caused by AD or introduced by confounding factors of AD and CVD. Understanding the causal relationship between AD and CVD could have implications for appropriate identification, clinical surveillance, and management of high-risk population. Mendelian randomization (MR) analysis is a novel epidemiological approach to assess the causal relationship between an exposure and an outcome [12], with less susceptibility to unmeasured confounders and reverse causation by using genetic variants (i.e., single nucleotide polymorphisms, SNPs) as instrumental variables (IVs) [13,14].

Objectives

In this study, we explored the causal associations between AD and CVD events using the MR method.

Methods

We carried out a two-sample MR analysis based on summary statistics to investigate the causal relationship between AD and CVD events including stroke, heart failure, CAD, myocardial infarction, and angina pectoris. Single nucleotide polymorphisms (SNPs) were selected as instruments variables because they are randomly allocated and less probable to be affected by confounding or reverse causation [13]. We used publicly available data, informed patients consents and ethical approvals were available in original genome-wide association studies (GWAS) studies.

Data Sources and Selection of SNPs

Summary-level data for AD were extracted from the EARly Genetics and Lifecourse Epidemiology (EAGLE) eczema consortium, including 13,287 cases and 41,345 controls of mostly European ancestry [16]. Summary-level data stroke were extracted from the MEGASTROKE Consortium, a meta-analysis of 29 GWAS including a total of 40,585 cases and 406,111 non-cases of European ancestry [17]. Summary-level data for heart failure were extracted from the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) Consortium [18], comprising 47,309 cases and 930,014 non-cases of European ancestry across 26 studies. Summary-level data for CAD from UKBiobank included 10801 cases and 137914 non-cases of European ancestry [19]. Summary-level data for myocardial infarction from UKBiobank included 4837 cases and 332,362 non-cases of European ancestry. Summary-level data for angina pectoris from UKBiobank included 4,837 cases and 332,362 non-cases of European ancestry.

Statistical Analysis

For each CVD outcome, we carried out two-sample MR analysis to estimate the causal effect of AD, using the “TwoSampleMR” package of R. The inverse-variance weighted (IVW) linear regression was conducted as the primary analysis. IVW is an efficient analysis method which assumes that all genetic variants are valid IVs, and that there is no horizontal pleiotropy [20]. We calculated the odds ratio (OR) with 95% confidence interval (CI) and created the SNP effect scatter plot.

Besides, we assessed the potential violations of the assumptions of MR analysis by performing a number of complementary sensitivity analysis: weighted median approach for examining result robustness when some instruments may be potentially invalid [20], MR-Egger regression for evaluating the directional pleiotropy of instruments [21,22], weighted mode, which generally has low bias and low Type I error rate inflation [23], MR Pleiotropy RESidual Sum and Outlier (MR PRESSO) for outlier instrument detection [24], and leave-one-out analysis to evaluate whether the MR estimate was influenced by single proxy SNP. We also calculated the Cochran Q test from the IVW analysis to examine potential horizontal pleiotropy.

All statistical analyses were performed using R software 4.0.3 (R Foundation for Statistical Computing). All statistical tests were two-sided with \( \alpha = 0.05 \).

Results

Genetic Instruments

Thirteen SNPs were identified as associated with AD (\( P<5\times10^{-8} \)), with independent inheritance (\( r^2<0.01 \)), and without linkage disequilibrium (LD) in summary statistics. All of these 13 SNPs were available in GWAS for stroke, heart failure, CAD, myocardial infarction, angina pectoris. Details of the included SNPs are shown in Tables S1, Tables S2, S3, S4, and S5 respectively.
Two-sample MR of AD and CVD

No significant evidence was found for a causal effect of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris using the IVW analysis (stroke: OR = 1.03, 95%CI: 0.97-1.09, P = 0.363; heart failure: OR = 1.04, 95%CI: 0.99-1.09, P = 0.119; CAD: OR = 1.00, 95%CI: 0.94-1.06, P = 0.961; myocardial infarction: OR = 1.00, 95%CI: 1.00-1.00, P = 0.322; angina pectoris: OR = 1.00, 95%CI: 1.00-1.00, P = 0.369). The results neither weighted median, MR Egger, weighted mode nor MR PRESSO analyses were significant for all of the diseases above (Table 1 and Figures S1, S2, S3, S4, S5).

Leave-one-out analysis indicated no influence of single SNP on the risk estimates of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris. P values of Cochrane Q test and MR Egger intercept for AD on stroke were 0.481 and 0.695, respectively; for AD on heart failure were 0.150 and 0.224, respectively; for AD on CAD were 0.146 and 0.583, respectively; for AD on myocardial infarction were 0.417 and 0.993, respectively; for AD on angina pectoris were 0.080 and 0.752, respectively, suggesting no evidence of potential horizontal pleiotropy and heterogeneity.

Conclusions

To the best of our knowledge, this is the first study to explore the causal relationship between AD and CVD based on an MR approach. Our results did not support a causal effect of AD on CVD.

Previous studies on the link between AD and stroke are controversial. In a Danish matched cohort study, patients with severe AD had an increased risk of ischemic stroke, but after adjustment for socioeconomic status, smoking, comorbidities, and medication use, the risk was similar with controls [6]. In a cohort from the Nurses’ Health Study 2, the risk of stroke was significantly increased in female nurses with AD in the age and models adjusted for demographic, lifestyle risk factors, family history of MI, and

Table 1. The Causal Effect of Atopic Dermatitis on Stroke

<table>
<thead>
<tr>
<th>Type of CVD</th>
<th>Method</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>No. of SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>IVW</td>
<td>1.03 (0.97-1.09)</td>
<td>0.363</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>0.99 (0.92-1.05)</td>
<td>0.681</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>0.96 (0.79-1.17)</td>
<td>0.694</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted mode</td>
<td>0.97 (0.88-1.07)</td>
<td>0.529</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR PRESSO</td>
<td>1.01 (0.96-1.06)</td>
<td>0.659</td>
<td>13</td>
</tr>
<tr>
<td>Heart failure</td>
<td>IVW</td>
<td>1.04 (0.99-1.09)</td>
<td>0.119</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>1.05 (1.00-1.11)</td>
<td>0.069</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>1.13 (0.98-1.30)</td>
<td>0.110</td>
<td>13</td>
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<tr>
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<td>1.06 (0.98-1.14)</td>
<td>0.176</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR PRESSO</td>
<td>1.04 (0.99-1.09)</td>
<td>0.145</td>
<td>13</td>
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<td>Coronary artery disease</td>
<td>IVW</td>
<td>1.00 (0.96-1.05)</td>
<td>0.988</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>0.99 (0.94-1.05)</td>
<td>0.760</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>0.96 (0.84-1.10)</td>
<td>0.608</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted mode</td>
<td>0.98 (0.90-1.07)</td>
<td>0.654</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR PRESSO</td>
<td>1.00 (0.96-1.05)</td>
<td>0.988</td>
<td>13</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>IVW</td>
<td>1.00 (1.00-1.00)</td>
<td>0.322</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>1.01 (1.00-1.00)</td>
<td>0.789</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>1.00 (1.00-1.00)</td>
<td>0.724</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted mode</td>
<td>1.00 (1.00-1.00)</td>
<td>0.574</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR PRESSO</td>
<td>1.00 (1.00-1.00)</td>
<td>0.328</td>
<td>13</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>IVW</td>
<td>1.00 (1.00-1.00)</td>
<td>0.369</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted median</td>
<td>1.01 (1.00-1.00)</td>
<td>0.416</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR Egger</td>
<td>1.00 (1.00-1.00)</td>
<td>0.992</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Weighted mode</td>
<td>1.00 (1.00-1.00)</td>
<td>0.627</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>MR PRESSO</td>
<td>1.00 (1.00-1.00)</td>
<td>0.386</td>
<td>13</td>
</tr>
</tbody>
</table>

CI = Confidence interval; CVD = cardiovascular disease; IVW = inverse variance-weighted; MR = mendelian randomization; OR = odds ratio; SNP = single-nucleotide polymorphism.
postmenopausal hormone replacement use. However, after further controlling for hypertension, hypercholesterolemia, and diabetes, the association between AD and stroke was no longer significant [7]. In a Swedish nationwide case-control study, only severe AD was associated with ischemic stroke [8]. A cross-sectional study conducted among primary care and community settings patients found only adult patients with moderate to severe AD was significantly associated with higher prevalence rates of prior stroke compared to the control: 4.4% versus 2.4% [25]. In a large population-based study including three surveys in US, AD was not associated with stroke in NHANES 2005-2006, but was significantly associated with higher odds of stroke in NHIS 2010 and 2012 in crude models and multivariate models adjusted for demographic, lifestyle factors, hay fever and asthma [9]. A population-based cohort study with data from the UK Clinical Practice Research Datalink reported very modest association between AD and stroke in adjusted models, and the associations were considerably stronger in patients with severe or active AD [10]. Two recent large German studies also found no association between AD and stroke [26,27]. Moreover, a large Canadian cohort even found AD was associated with lower risk of stroke in adjusted model [28].

Though there are only few studies on the link between AD and heart failure, the results are still inconsistent. An US cross-sectional inpatient study reported a significant relationship between AD and heart failure [29]. A cohort study also found positive association between AD and heart failure [10].

CAD is a cause of major morbidity and mortality worldwide. It includes stable ischemic heart disease, MI and unstable angina [30]. Several studies provided estimates for the association of AD with the risk of CAD. The abovementioned study conducted by Silverberg et al. showed AD was associated with significantly higher odds of CAD, the associations attenuated but remained significant in the three adjusted models [9]. But Kwa et al. study reported AD was not significantly associated with CAD [29]. Findings about associations between AD and angina were also mixing. Standl et al. and Silverwood et al. reported a significantly positive association between AD and angina [10,26]. However, AD was not found to be significantly associated with angina in NHANES [9]. The situation is similar to MI. There is a significant association between AD and MI in NHANES, but after controlling risk factor of CVD, the association did not remain significant [9]. Studies of Drucker et al. and Standl et al. also suggested no evidence of the association between AD and MI [7,26,28]. However, Silverwood et al., the NHIS 2010, and a recent cross-sectional study suggested AD was associated with an increased risk of MI, even adjusted for potential confounding factors [9,10,31]. AD and CVD related studies are shown in Table S6.

There are some limitations to the present study. First, the summary-level GWAS data we used were based mainly on people of European ancestry. Therefore, results in this study may not be applicable to other populations. Second, onset age and disease severity of AD might influence the association between AD and comorbidities, but because the limitation of data, we were not able to perform subgroup analyses by age and severity of AD. Third, an important limitation for MR study is potential pleiotropy. In this study, we applied various MR approaches to test for potential pleiotropy, and no evidence of pleiotropy for all the analyses was observed. Moreover, the definitions of AD and comorbidities used in the data is a mixture of self-reported diagnosis together with doctor diagnosed cases, which may cause bias to our findings.

Conclusion
In conclusion, MR study does not support a causal effect of AD on stroke, heart failure, CAD, myocardial infarction, angina pectoris.

References


Patient Use of Complementary and Alternative Medicine for Psoriasis Vulgaris and Factors Believed to Trigger the Disease: a Multicenter Cross-Sectional Study With 1621 Patients

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Key words: psoriasis vulgaris, complementary and alternative medicine, diet, stress, gluten


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Introduction

Complementary and alternative medicine (CAM) is defined as various medical and healthcare systems, practices, and products that are currently outside the scope of standard medical therapy [1,2]. This definition includes treatment methods used instead of conventional treatments, as well as those used as accessory or complementary to conventional treatments [3].

Interest in CAM methods, which date back centuries, is increasing day by day. One of the reasons for this is easy access information about these methods with the introduction of the internet into daily life. Another reason is that modern treatments are expensive since they enter the market after extensive research and experiments, and substantial information is available concerning possible serious side effects [4]. The use of CAM for any reason is seen in almost one in two people, and this rate further increases in individuals with chronic diseases [4,5].

Although the frequency of CAM use due to dermatological diseases varies from one country to another, it is reported globally to range from 28.9% to 69% [6,7]. The most commonly used CAM methods in dermatological diseases worldwide have been reported as homeopathy, herbal treatments, and other food supplements [5]. However, these preferences can also differ according to the geographical area. It has been reported that the patient groups that most resort to CAM are those suffering from psoriasis, acne, alopecia, and verruca [8].

Psoriasis vulgaris (PV) impairs the quality of life (QoL) and psychological state of patients due to its repetitive nature, ability to settle in specific parts of the body such as the face and genitals, accompanying comorbidities, and persistence for many years if left untreated. Patients sometimes refer to CAM methods because they are tired of conventional treatments and/or disease recurrence or they experience side effects related to medical treatments.

In the current study, we aimed to determine the frequency of CAM use in PV patients, preferred CAM methods, their reasons to refer to these methods, whether they would recommend CAM to other patients, and factors that they thought worsened their disease. To our knowledge, this study was conducted with the largest sample to investigate this topic and represents the whole society with a holistic approach with the participation of PV patients from all regions of Turkey.

Methods

Study Population

The study included voluntary literate at least 18-years-old PV patients who were followed-up in 18 different dermatology outpatient clinics in different regions of Turkey between January 1, 2020 and July 1, 2020. The patients signed a statement of written informed consent about the study.
**Procedure**

The study approval was obtained from the university ethical committee (18.12.2019/0528). The study protocol was registered at https://www.clinicaltrials.gov with the number NCT04207216. The survey items were prepared by the researchers who planned the study. The Psoriasis Area Severity Index (PASI) and clinical data concerning the disease were noted by the physicians. Then, the patients were asked to complete the survey and the Dermatology Life Quality Index (DLQI) without time limitation [9,10]. The survey questions are shown in Supplementary Table.

**Statistical Analysis**

The study data were analyzed using the SPSS IBM software package (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0.). The results were obtained at the 95% confidence level. Demographic data and other measurements were expressed using descriptive statistics, average, and percentage values. Among the patients with a history of CAM use, age, PASI, DLQI, duration of illness, and amount of smoking were tested with the independent samples t-test, and the remaining variables were evaluated with the chi-square test.

**Results**

A total of 1,621 patients, 741 women, and 880 men, were included in the study. The demographic characteristics of the patients are summarized in Table 1. 916 patients (56.51%) had used CAM for PV at some time in their lives.

Considering the seven regions of Turkey, CAM use was high in the Marmara region (29.1%), in which the population is more educated and has higher income, and this was followed by the central Anatolia region (13.9%) where the capital, Ankara, is located. Considering the treatments that had been used or were currently used by the patients, CAM

---

**Table 1. CAM use of the patients according to their demographic characteristics and disease involvement.**

<table>
<thead>
<tr>
<th></th>
<th>CAM use present</th>
<th>CAM use absent</th>
<th>P</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Age</td>
<td>Mean</td>
<td>42.54 ± 15</td>
<td>45.71 ± 12</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>415</td>
<td>56.01</td>
<td>326</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>501</td>
<td>56.93</td>
<td>379</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>654</td>
<td>55.52</td>
<td>524</td>
</tr>
<tr>
<td></td>
<td>Single</td>
<td>218</td>
<td>59.89</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>Divorced</td>
<td>42</td>
<td>57.53</td>
<td>31</td>
</tr>
<tr>
<td>Education level</td>
<td>Literate, primary or middle school</td>
<td>359</td>
<td>53.03</td>
<td>318</td>
</tr>
<tr>
<td></td>
<td>High school, college</td>
<td>340</td>
<td>56.86</td>
<td>258</td>
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<td>200</td>
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<td>207</td>
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<td></td>
<td>Above $1300</td>
<td>46</td>
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<tr>
<td>PASI</td>
<td>Mean</td>
<td>6.5 ± 6.1</td>
<td>5.8 ± 6.2</td>
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<td>DLQI</td>
<td>Mean</td>
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<td>Disease duration (years)</td>
<td>Mean</td>
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<td>14 ± 11</td>
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<td>530</td>
<td>59.42</td>
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<td>386</td>
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<td>Alcohol consumption</td>
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<td>56.51</td>
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</tr>
<tr>
<td>Family history of psoriasis</td>
<td>Absent</td>
<td>355</td>
<td>58.58</td>
<td>251</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>557</td>
<td>54.88</td>
<td>452</td>
</tr>
</tbody>
</table>

Table 1 continues
**Table 1. CAM use of the patients according to their demographic characteristics and disease involvement. (continued)**

<table>
<thead>
<tr>
<th>CAM use present</th>
<th>CAM use absent</th>
<th>P</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Joint pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain present, no arthritis</td>
<td>238</td>
<td>62.30</td>
<td>144</td>
</tr>
<tr>
<td>Pain and arthritis present</td>
<td>115</td>
<td>62.16</td>
<td>70</td>
</tr>
<tr>
<td>Absent</td>
<td>561</td>
<td>58.68</td>
<td>488</td>
</tr>
<tr>
<td>Nail involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>525</td>
<td>54.63</td>
<td>436</td>
</tr>
<tr>
<td>Present</td>
<td>391</td>
<td>59.24</td>
<td>269</td>
</tr>
<tr>
<td>Scalp involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>393</td>
<td>55.20</td>
<td>319</td>
</tr>
<tr>
<td>Present</td>
<td>523</td>
<td>57.54</td>
<td>386</td>
</tr>
<tr>
<td>Facial involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>720</td>
<td>54.71</td>
<td>596</td>
</tr>
<tr>
<td>Present</td>
<td>196</td>
<td>64.26</td>
<td>109</td>
</tr>
<tr>
<td>Hand involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>569</td>
<td>56.06</td>
<td>446</td>
</tr>
<tr>
<td>Present</td>
<td>347</td>
<td>57.26</td>
<td>259</td>
</tr>
<tr>
<td>Genital involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>677</td>
<td>54.55</td>
<td>564</td>
</tr>
<tr>
<td>Present</td>
<td>238</td>
<td>62.80</td>
<td>141</td>
</tr>
<tr>
<td>Skin-fold involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>681</td>
<td>55.28</td>
<td>551</td>
</tr>
<tr>
<td>Present</td>
<td>235</td>
<td>60.41</td>
<td>154</td>
</tr>
</tbody>
</table>

Income level was calculated based on the exchange rate at the time of the study.
CAM = Complementary and alternative medicine; PASI = Psoriasis Area Severity Index; DLQI = Dermatology Life Quality Index.

Figure 1. CAM methods preferred by the patients. More than one response allowed (total percentage exceeds 100%). CAM = complementary and alternative medicine.

use was higher in the groups of cyclosporine (64.02%), biological agents (64%), phototherapy (62.87%), and methotrexate (60.78%).

The CAM methods preferred are summarized in Figure 1. They resorted to these methods most commonly after the fifth year of the disease (32%) and within the first to fifth years of the disease (27.3%). This was followed by the groups that started to use CAM methods from the time of diagnosis (18.8%), before consulting a doctor (11.24%), and within the first year of the disease (9.4%). The patients had mostly heard of CAM methods from their acquaintances (33.95%) or relatives (28.49%), and through the internet (23.91%). Those that heard from their dermatologists constituted 12.34% of the sample. The duration of CAM use was reported to be 1-6 months by 24.78% of the patients and 2-4 weeks by 24.56%. For 31.77% of the patients, the CAM practitioner did not have any CAM training while 33% did not know about the practitioner training and 31% were not
interested in the practitioner education. The patients most resorted to CAM methods when their disease became severe (46.40%) while 31.55% stated that they referred to these methods when they had mild PV, 24.56% when they experienced joint pain, 20.09% when the disease recurred, and 14.41% when they had no hope about getting better.

While 54.5% stated that they would not recommend these methods to other patients, 11.55% were positive about recommendation, and the remainder were indecisive. CAM had no effect on PV for 56.55% of the patients and worsened the disease according to 8.33% whereas 28.38% thought they had benefitted from treatment. The remainder made no comment about the effect of CAM on PV. The answers about the reason why they received CAM are summarized in Table 2.

The physicians of 67.03% of the patients did not ask whether they had used CAM, and 48.91% of the patients did not spontaneously inform their doctors that they had received such treatment. The patients who shared this information stated that their physicians recommended stopping the CAM treatment (27.65%), did not interfere (26.61%), or mentioned that there was no harm in continuing to use CAM (20.79%). The remaining 24.95% did not care or were unresponsive.

When the patients that had not used CAM were asked for their views concerning these methods, 56.17% did not find them reliable and safe, 28.94% thought they were nonsensical and useless, 28.37% found them expensive, and 24.26% were concerned about side effects. When asked whether they would use CAM in the future, 60.85% stated that they would not use them, 25.39% would use if they were sure they would do no harm, 23.12% might use, and 6.95% were thinking about using them.

56.69% of the patients thought that various foods affected PV while 28.74% did not consider that any food or habit had a worsening effect on PV. The patients thoughts on which food and habits are affecting psoriasis are listed in Table 3.

A gluten-free diet was followed by 5.55% of the patients at some time in their lives. Of the patients with this history, 52.22% thought that removing gluten from their diet did not affect their PV symptoms while 21.11% believed that it helped relieve their rash, 26.67% itch, 4.44% joint pain, 5.56% nail symptoms.

### Conclusions

In previous studies conducted with psoriasis patients, the use of CAM was reported at a rate of 41%-69% [11-18]. Our rate of 56.51% was similar to previous studies. In addition, there was no significant difference in CAM use according to gender and financial status, which is in agreement with the literature [17]. In the current study, the patients using CAM were significantly younger (42.5 and 45.7 years, respectively; P = 0.000) and had a significantly longer mean disease duration (15.8 and 14.3 years, respectively, P = 0.007) compared to those without a history of CAM use, which is also consistent with previous research [12,17]. Generally, people that were younger but who had a longer disease duration were determined to seek alternative treatment options.

In our study, the patients with a minimum university level tended to have a higher rate of CAM use. This contradicts with a previous study indicating no relationship between education level and CAM use [16]. In Turkey, individuals with higher education participate more in work life and they are more likely to do an online research and access these methods. This may contribute to higher use of CAM in our highly educated patients.

The patients using CAM had significantly higher PASI and DLQI than those that did not use (PASI = 6.5 and 5.8, respectively; DLQI = 10.2 and 8.3, respectively). Previous studies

<table>
<thead>
<tr>
<th>Reason for Receiving CAM</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saw no benefit of modern drugs for psoriasis</td>
<td>177</td>
<td>19.32</td>
</tr>
<tr>
<td>Thought it would prevent disease recurrence</td>
<td>242</td>
<td>26.42</td>
</tr>
<tr>
<td>Became tired of medical therapies and decided to look for an alternative method</td>
<td>334</td>
<td>36.46</td>
</tr>
<tr>
<td>Natural and safe with no side effect</td>
<td>275</td>
<td>30.02</td>
</tr>
<tr>
<td>Cheaper</td>
<td>33</td>
<td>3.6</td>
</tr>
<tr>
<td>More reliable and effective than medical therapies</td>
<td>18</td>
<td>1.97</td>
</tr>
<tr>
<td>Easily available</td>
<td>64</td>
<td>6.99</td>
</tr>
<tr>
<td>Don’t know</td>
<td>111</td>
<td>12.12</td>
</tr>
<tr>
<td>Other</td>
<td>68</td>
<td>7.42</td>
</tr>
<tr>
<td>Total</td>
<td>1322</td>
<td></td>
</tr>
</tbody>
</table>

More than one response allowed (total percentage exceeds 100%).
CAM = complementary and alternative medicine.
CAM use varies by country and culture. Patients often try treatments that are easier to access in areas where they live. Our patients mostly used herbal topicals (45.52%), food supplements (31.0%), and hot springs/baths (26.86%) while they least referred to hypnosis and homeopathy treatments, which are not common in Turkey. Previous studies showed that herbal topicals (36.80-73.13%) were among the most preferred CAM method [11,12,14-18,20]. In addition, as in our study, food supplements were among the frequently preferred CAM methods in many studies [14,17]. This shows that despite differences depending on the geography, patients tend to rely more on drugs derived from plants. Herbal treatments are also officially accepted in Far Eastern countries. In Korea, all herbal, acupuncture and bath treatments are classified under the name of oriental therapy and subject to license, and their use is legally approved [15]. Herbal medicine formulas are included in traditional Chinese treatments and used for psoriasis [21]. Since natural spring waters are similarly reported a higher rate of CAM use in patients with high PASI scores [12,16,18]. This suggests that as the disease duration and severity increase and the QoL deteriorates, patients are more willing to try different treatment options.

QoL in PV patients may vary according to the involvement areas. In our study, CAM use was significantly higher in those with facial (64.26%) and genital involvement (62.8%) and those with arthralgia (62.30%) and arthritis (62.16%). In another study, CAM use was found to be high in the presence of scalp and facial involvement [18]. Previous publications did not detect a difference in the use of CAM among patients with arthritis [17,18]. Psychosocial effects are more commonly observed in patients with lesions located in visible areas and intimate areas, as well as those with arthropathic psoriasis [19]. This situation may also create an important barrier for patients to present to health institutions to be examined by physicians and explain why our patients felt the need to refer to CAM methods.

| Table 3. Patients thoughts on food and habits affecting psoriasis. |
|---------------------------------|--------|--------|
| Sunflower seeds                  | 222    | 13.70  |
| Nuts                             | 141    | 8.70   |
| Hot-tasting food                 | 510    | 31.46  |
| Spicy food                       | 489    | 30.17  |
| Milk, dairy products             | 30     | 3.08   |
| Packaged food, such as crisps    | 233    | 14.37  |
| Fried food                       | 285    | 17.58  |
| Offal                            | 31     | 1.91   |
| Food and beverages with coloring, such as coke | 238 | 14.68 |
| Sugar, chocolate                 | 142    | 8.76   |
| Fatty food                       | 171    | 10.55  |
| Chicken                          | 28     | 1.73   |
| Red meat                         | 61     | 3.76   |
| Fish, fish oil                   | 23     | 1.42%  |
| Hormone-injected vegetables/fruit| 69     | 4.26   |
| Alcohol                          | 228    | 14.07  |
| Wheat, wheat products            | 51     | 3.15   |
| Eggplant                         | 136    | 8.39   |
| Tomato                           | 365    | 22.52  |
| Ketchup, mayonnaise              | 107    | 6.60   |
| Paste, sauces                    | 163    | 10.06  |
| Smoking                          | 280    | 17.27  |
| Gluten                           | 54     | 3.33   |
| Stress                           | 563    | 34.73  |
| Lack of sleep                    | 202    | 12.46  |
| Other                            | 88     | 5.43   |
| Total                            | 4930   |        |

More than one response allowed; total percentage exceeds 100%.
abundant in Turkey, bath/spa treatments are among the frequently preferred treatments. Similarly, studies conducted in Korea (44.3%) and Israel (46%) reported that bath/spa treatments were used frequently [12,15]. In addition, herbal products and salts used in bath were frequently preferred methods in other studies [16,17].

Among the reasons for using CAM, our patients commented that they sought an alternative treatment method (36.46%), considered it natural (30.02%), and thought it would prevent PV recurrence (26.42%). Nineteen percent considered that the modern drugs did not help. In general, it was seen that the patients were worn-out due to the repetitive nature of psoriasis and referred to CAM with the hope of achieving a full cure. In addition, there were many patients that believed that these treatments had no side effects or health risk. Similarly, in previous studies, patients frequently stated that they resorted to CAM methods because they try everything to eliminate their disease, were unhappy with conventional treatments’ results, and found CAM to be safe [12,15-17,22].

Although our patients mostly received recommendations for CAM treatments from their acquaintances (33.95%), some also read about them on the internet (23.91%) and were recommended by their dermatologists (12.34%). In previous studies, patients generally found out about CAM through their acquaintances, friends and the internet, with dermatologist recommendations being reported at a rate of only 3.40%-4.48% [15,17]. This difference can be attributed to the varying practices of physicians in terms of CAM use and recommendations according to geographical differences.

Thirty-five percent stated that stress was the factor that most worsened PV. This was followed by those considering that the consumption of hot and spicy foods, tomatoes, and smoking had a negative effect on psoriasis. The rate of those who thought that their food preferences did not affect was 43.31%. Afifi et al reported this rate to be 37% and determined sugar (13.8%) and tomato (7.4%) to be the food that most increased the disease severity [23]. A considerable proportion of our patients (22.52%) thought that tomato worsened their symptoms, but there was a higher rate of those considering hot (31.46%) and spicy (30.17%) foods to have a negative effect, which was much higher than reported before (2%-5%) [23]. Since dietary habits can differ between countries, the higher rate of our patients believing that hot and spicy foods and tomato worsened their disease compared to previous studies can be explained by the more frequent consumption of such food products in Turkey.

There are different opinions about the relationship between psoriasis and gluten. In contrast to those that claim that there is no relationship between gluten intake and the risk of developing psoriasis, there are also publications that link celiac disease with PV [24-27]. In a previous study, 52.9% of PV patients who followed a gluten-free diet reported that they observed some improvement in their disease [23]. In our sample, 52.22% following a gluten-free diet did not consider any effect on psoriasis while 3.33% of all patients thought that gluten exacerbated PV. This is lower than the rate of those reporting that gluten affected their disease (7.2%) in a USA study [23].

Although most physicians do not pay any attention to CAM treatments, there are many studies on this subject in the literature. Cochrane reviews, meta-analyses and systematic reviews reveal the presence of studies investigating products containing fatty-acid containing oils, oral and topical herbal medicine, marine medicines such as fish oil, acupuncture, selenium, vitamin D, zinc, avocado oil, climatotherapy, and mind/body interventions in the psoriasis treatment [21,18-31]. These studies report findings of anti-inflammatory, antiproliferative and immunomodulatory effects of the herbal treatments as a complementary option to conventional therapies [28]. However, it is advised that care should be taken in terms of hepatotoxicity, and the benefits of these treatments are low and the methodologies of these studies are usually weak [21,28]. It is also suggested that there is no solid evidence concerning the benefits of vitamin D, zinc, selenium, topical vitamin B12, and avocado oil while evidence presented on oil, aloe vera, fish oil, climatotherapy and mind/body interventions is conflicting, and acupuncture is not effective [29].

In our study, 67.03% of the patients stated that their physicians did not inquire about their CAM use, and 48.91% did not inform them about CAM use if not prompted by their physicians. As a result, it was seen that most physicians were unaware of CAM being used by their patients. CAM use without the physician knowledge can lead to undesirable side effects and make it difficult for the physician to determine the underlying cause of these effects. Similar to our results, a previous study reported that the rate of physicians asking their patients about CAM use was very low (10%) and only 22% of the patients shared this information with their physicians [12].

Due to the chronic and recurrent nature of PV, more than half the patients seek CAM methods. This tendency is more common in patients with a severe disease, poorer QoL, increased disease duration, arthritis/arthralgia, and facial, genital involvement. We determined that the patients used CAM because they thought that these methods were natural and safe and had no side effects, and they were exhausted with the process of undergoing conventional treatments and experiencing disease recurrence. Herbal topicals, food supplements and bath/spa treatments were the most preferred CAM methods. The physicians usually did not ask about their patients CAM use, and almost half of the patients did not choose to share this information with their physicians.
The patients considered that stress, consumption of hot and spicy foods, and smoking worsened their disease, and gluten did not effect. In light of these data, it is considered very important that the physicians should question the use of CAM in their patients with chronic diseases and guide them appropriately.

References


Papulopustular Rosacea Treated With Ivermectin 1% Cream: Remission of the Demodex Mite Infestation Over Time and Evaluation of Clinical Relapses

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Key words: ivermectin, rosacea, papulopustular rosacea


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ABSTRACT

Introduction: Topical ivermectin is an anti-inflammatory and anti-Demodex drug for papulopustular rosacea. Rosacea is a relapsing disease and the time between recurrences should be considered alongside efficacy.

Objectives: The aims of this study were to assess the time of first relapse and relapse rates of Demodex mite infestation and papulopustular rosacea.

Methods: We conducted a prospective study of subjects affected by different degrees of papulopustular rosacea. Patients that achieved a complete response after treatment were monitored every 4 weeks and up to 32 additional weeks. For each patient, we evaluated recording the time to first relapse and relapse rate of Demodex mite infestation and rosacea.

Results: The overall success rate on Demodex infestation was 87.5% only 12.5% relapse. Ivermectin leads to complete response in 70% of patients. Median time to relapse was 140 days, the mean time was 152 days. The global success rate was 54.76%.

Conclusions: Topical ivermectin keeps a remission of Demodex infestation and clinical remission for long time. We proposed a twice weekly ivermectin maintenance therapy to reduce recurrences.
**Introduction**

Rosacea is a chronic, inflammatory skin disease that starts between 30-50 years of age with a large prevalence in the general population [1]. Papulopustular rosacea (PPR) is characterized by multiple small dome-shaped erythematous papules and pustules arising on erythema in a centrofacial distribution [2].

Topical ivermectin cream 1% (IVM) is a drug characterized by both antiparasitic and anti-inflammatory effects [3-7], which gained the Food and Drug Administration (FDA) approval for the treatment of PPR in December 2014, and by European Medicines Agency (EMA) in March 2015 [5].

**Demodex** mites are standing human ectoparasites that have a higher concentration in PPR (a mean of 12.8 D/cm²) [8] than other people. Demodicosis in humans is associated with the common inflammatory skin condition rosacea but also with pityriasis folliculorum, where it is not accompanied by inflammation, and with other rarer clinical settings, including patients with symptoms of perioral dermatitis [9, 10] and granulomatous rosacea [11].

Although is well know the anti-parasitic effect of ivermectin, up to now, there are not studies that consider the time of relapse and relapse rates of Demodex mite infestation in patients affected by rosacea and treated with ivermectin.

Following the onset of the disease, patients with rosacea will experience cycles of relapse and remission of symptoms through their lives [3]. There are only very few studies that have analyzed patterns of relapse in moderate-to-severe and mild-to-moderate PPR treated with ivermectin [3, 12].

**Objectives**

The main aim of this study was to assess the time of first relapse and relapse rates of Demodex mite proliferation after interruption of ivermectin therapy [13]. The secondary goal was to study the time to first clinical relapse and relapse rates in patients affected by almost clear, mild and moderate PPR.

**Methods**

The prospective study was conducted at the Dermatology Centre of Ospedale Policlinico San Martino IRCCS in Genoa (Italy) from May 1st, 2020 to May 31st, 2021 on subjects suffering from papulopustular rosacea. Diagnosis of rosacea was made by an experienced dermatologist and based on the following National Rosacea Society (NRS) expert panel criteria [1]:

1. fixed centrofacial erythema in a characteristic pattern that may periodically intensify
2. papules and pustules (with or without telangiectasias, flushing and ocular manifestations) [14]

Subjects that had been treated with topical and systemic therapies during the previous year were not included in the study. For each patient, disease severity was assessed by Investigator Global Assessment score (IGA score) [11]. IGA score defines disease severity from 0 to 4: IGA 0 = no inflammatory lesions, no erythema; IGA 1 = very few small papules/pustules, very mild erythema; IGA 2 = few small papules/pustules, mild erythema; IGA 3 = several small or large papules/pustules, moderate erythema; IGA 4 = numerous small or large papules/pustules, severe erythema [15].

In order to study Demodex mites count, a standardized skin surface biopsy (SSSB) was performed by a trained dermatologist on the target area [8]. SSSB is a sampling method in which 1 cm² of the superficial layer of the stratum corneum and its follicular content is recovered for analysis [8]. Samples obtained by SSSB were examined with an optical microscope at × 10 and × 40 magnifications. Samples with ≥5 Demodex/cm² (D/cm²) was considered positive (D+) [8]. Antiparasitic efficacy assessments were time to first relapse and relapse rate of positive SSSB test.

We defined a successful therapeutic intervention when patients affected by IGA 1, 2 and 3 rosacea at baseline achieved IGA= 0 after 16 weeks of therapy. After this treatment period, patients that achieved IGA=0 were followed every 4 weeks for up to 32 additional weeks (Weeks 16-48) [3].

Efficacy assessments were the time to first relapse and relapse rate [3]. Time to first relapse was defined as the time relapse between Week 16 (end of treatment) and the first relapse (IGA ≥1) during follow up. Relapse rate was defined as the percentage of patients who relapsed within the course of the 32 weeks.

Descriptive statistical analyses were performed, and data were shown as median (range), mean (SD), or number (percentage). Relapse rates and time to relapse were evaluated for patients divided for IGA score and analyzed using the Kaplan-Meier method and log-rank test. Patients who relapsed were considered censored in the analysis. For categorical variables, data were analyzed using the χ² test and Fisher exact test.

The study was approved by the local Ethical Review Board (Comitato Etico Regione Liguria. N. Registro CER Liguria: 467/2021 – DB id 11726)

**Results**

We recruited 60 Caucasian patients, including 45 women (75%) and 15 men (25%) with a mean age of 57 years (SD 11.2, range 30-81 years). Demographic and clinical data are summarized in Table 1. Thirty-one/60 patients (51.67%) had an IGA score 1, 16/60 patients (26.67%) had an IGA score 2 and 13/60 (21.66%) had an IGA score 3.
**Demodex Mite Density**

Using SSSB, Demodex mites were found (D+) in 20/60 (33.33%) patients of whom 7 had IGA 1, 7 had IGA 2 and 6 had IGA3. After 16 weeks of therapy, SSSB resulted negative (D-) in 16/20 (80%) of whom 5/7 (71.43%) had IGA 1, 6/7 (85.71%) had IGA2 and 5/6 (83.33%) had IGA3. There are not statistical differences to become D- (P > 0.999, P > 0.999, P > 0.999) after 16 weeks of therapy.

**Relapse Evaluation and Demodex Mite Infestation**

Only 2/16 (12.5%) IGA 2 PPR D- relapsed after 224 days. The global success rate of Demodex infestation was 87.5%. Regarding 4 D+ patients positive after 16 weeks of therapy, 2/4 achieved D- at Day 150, ¼ at Day 224 while ¼ remained D+.

**IGA Score and Effectiveness**

Patients that reached IGA=0 after 16 weeks of treatment are summarized in Table 1. There are not statistical significative differences to achieve IGA = 0 among IGA1-2-3 at baseline (P = 0.725, P = 0.1552, P = 0.47, respectively).

**Relapse Evaluation**

Kaplan-Meier curves show no different median time of first relapse (IGA ≥ 1) among IGA 1-2-3 (P log rank test = 0.551) (Figure 1). At week 48, the percentages of patients who experienced a relapse (IGA ≥ 1) after discontinuation of ivermectin treatment (relapse rate) was 45.24%, and in particular, they were 45.83% for IGA1, 45.43% for IGA 2 e 28.57% for IGA 3. The global success rate (percentage of patients who reached 0 at the end of treatment) was 54.76% and in particular, they were 54.17% for IGA1, 54.54% for IGA 2 and 71.43% for IGA3. Median time to relapse was 140 days (84-224 days), in particular, 154 days (range: 84-224) for IGA 1, 196 days (range: 98-224) for IGA 2, 105 days (range: 98-112) for IGA 3. The mean time to relapse was 152.44 ± 51.47 days, in particular, 154 ± 58.57 days for IGA 2 and 105 days ± 9.90 days for IGA 3.

**Table 1. Demographic and Clinical Data of Patients Divided by IGA Score.**

<table>
<thead>
<tr>
<th>Age, years, mean (SD)</th>
<th>IGA 1 (31)</th>
<th>IGA 2 (16)</th>
<th>IGA 3 (13)</th>
<th>Total (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58 (10.1)</td>
<td>56 (14.0)</td>
<td>57 (9.5)</td>
<td>57 (11.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>20 (64.52)</td>
<td>13 (81.25)</td>
<td>12 (92.31)</td>
<td>45 (75)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>11 (35.48)</td>
<td>3 (18.75)</td>
<td>1 (7.69)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Patients reaching IGA= 0 at 16 weeks, N (%)</td>
<td>24 (77.42)</td>
<td>11 (68.75)</td>
<td>7 (53.85)</td>
<td>42 (70)</td>
</tr>
<tr>
<td>Patients positive for Demodex at baseline, N (%)</td>
<td>7 (22.58)</td>
<td>7 (43.75)</td>
<td>6 (46.15)</td>
<td>20 (33.33)</td>
</tr>
<tr>
<td>Patients negative for Demodex at 16 weeks, N (%)</td>
<td>5 (16.13)</td>
<td>6 (37.5)</td>
<td>5 (38.46)</td>
<td>16 (26.67)</td>
</tr>
</tbody>
</table>

IGA= Investigal Global Assessment; SD = standard deviation.

**Figure 1.** Time to first relapse of patients in ivermectin 1% cream. Kaplan-Meier plot demonstrates that there are not differences among patients treated with ivermectin divided to IGA score (P = 0.551).
Conclusions

Similarly, to previous study, we found 33% of Demodex positive samples at baseline [7]. The great anti-parasitic effect of ivermectin was confirmed by the overall success rate of Demodex infestation (87.5%). In the literature, there are not studies that consider the time of relapse and relapse rates of Demodex mite infestation in patients affected by rosacea and treated with ivermectin. In our study, we observed a low relapse rate of Demodex mite infestation (12.5%) in PPR showing as ivermectin has an excellent antiparasitic effect that last over time. It acts by blocking ligand-gated chloride channels, especially glutamate-gated anion channels in the peripheral nervous system of Demodex mites causing their paralysis and death [16]. The two patients that showed a relapse of Demodex mite infestation presented an erythematotelangiectatic rosacea (ETR) with few papules (Figure 2). This result is according to the hypothesis that ETR may be associated with non-visible Demodex proliferation, possibly corresponding to a subclinical stage of demodicosis [17-19]. Few papules may be an early sign of relapsed Demodex mite proliferation [20].

Our study confirms the efficacy of ivermectin 1% cream leading to complete response in 70% of almost clear, mild and moderate PPR after 16 weeks of therapy. Regarding relapses in patients with rosacea, a study from 2016 showing that patients affected by moderate-severe rosacea and treated with ivermectin had median times of first relapse significantly longer than those treated with metronidazole 0.75% cream (115 days versus 85 days) [3]. In addition, relapse rate was lower for patients previously treated with ivermectin 1% compared with metronidazole 0.75% (62.7% versus 68.4%) [3]. Dall’Oglio found only 2/20 mild and moderate PPR patients that relapsed [12]. In our study, we found a longer median time of first relapse (140 days) with a lower relapse rate (45.24%) than studies in the literature. As we have just shown, relapse rates are difficult to compare between different studies. We suppose that our results are better than those of Shaub et al because we considered mild forms instead of moderate-severe forms of rosacea baseline [3]. In fact, patients with IGA 3-4 rosacea had higher number of inflammatory lesions than patients with IGA 1-2 rosacea that keep clinical remission for longer days. Moreover, differences among studies could be justified by a different definition of relapse; while Shaub et al considered a relapse as IGA ≥ 2 we regarded as IGA ≥ 1 PPR [3]. This is because we take on IGA = 0 as desirable ideal goal of maintenance, crucial for patient’s outcome and for an effective improvement of his quality of life. However, patients that relapsed in our study showed mainly IGA = 1 PPR (22/27) without serious cases after suspension of therapy. Finally, the difficulties may also be due to the different follow-up periods. In fact, while we tracked our patients for 32 weeks, Shaub et al followed them for 36 weeks and Dall’Oglio for 12-to-24 weeks after treatment: a longer follow-up periods correspond to higher probability of relapse [3,12].

Since our results, ivermectin work with an anti-parasitic effect in Demodex positive PPRs eliminating mites as cause of inflammation and enabling a long remission of PPR with a low
risk of relapse. In addition, ivermectin acts as anti-inflammatory drug inducing a downregulation of the pro-inflammatory genes IL-8, human ß-defensin-3 (HBD3), Toll-like receptor-4 (TLR4), and tumor necrotic factor-alpha (TNF-α) [21], and by an inhibition of cathelicidin innate immune mediators, LL-37 and LLK5 in Demodex positive and negative PPRs [21,22]. We propose to keep a twice-weekly ivermectin maintenance therapy to reduce relapses, especially in Demodex negative rosacea where ivermectin only holds an anti-inflammatory effect. However, further studies are needed to evaluate the efficacy of maintenance therapy in patients treated with ivermectin.

Our study has different limitations: we did not have patients with severe rosacea and we did not evaluated patients with object instruments like erythema-directed digital photography. In conclusion, we confirm the anti-parasitic effect over time of ivermectin in PPR after cessation of the treatment. In addition, we demonstrate an extended clinical remission of cathelicidin innate immune mediators, LL-37 and KLK5 in Rosacea. We propose to keep a twice-weekly ivermectin maintenance therapy to reduce relapses, especially in Demodex positive and negative PPRs [21,22]. We propose to keep a twice-weekly ivermectin maintenance therapy to reduce relapses, especially in Demodex negative rosacea where ivermectin only holds an anti-inflammatory effect. However, further studies are needed to evaluate the efficacy of maintenance therapy in patients treated with ivermectin.

Our study has different limitations: we did not have patients with severe rosacea and we did not evaluated patients with object instruments like erythema-directed digital photography.

In conclusion, we confirm the anti-parasitic effect over time of ivermectin in PPR after cessation of the treatment. In addition, we demonstrate an extended clinical remission of PPR and we propose a twice-weekly ivermectin maintenance therapy to reduce clinical recurrences.

References
Clinico-epidemiological Aspects of Cutaneous Lesions in Injecting Drug Users Visiting an Oral Substitution Therapy Centre in Northern India: A Cross-Sectional study

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Key words: intravenous drug users, oral substitution therapy centers, skin manifestations, dermoscopic findings


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ABSTRACT

Introduction: Drug abuse has been taking a great toll on the health and well-being of the community for the past few decades. Substance abuse can lead to several cutaneous manifestations as direct injuries by the offending drug or the practices of drug usage cause secondary damage to the skin. The early recognition of these signs is of utmost importance to prevent long-term complications.

Objectives: To study the clinical-epidemiological profile of the skin diseases in Injecting Drug Users (IDU) attending an Oral Substitution Therapy (OST) Center in Northern India and to assess the psychological impact of skin conditions in IDUs attending OSTs.

Methods: This cross-sectional observational study involved 100 IDUs enrolled from the OST center who were subjected to brief history taking and clinical and dermoscopic evaluation of skin lesions. Dermatological quality of life index (DLQI), Depression, Anxiety, Stress Scale (DASS), and WHO-quality of life (QoL) questionnaire were used to evaluate the impact of skin lesions on psycho-social health and QoL of IDUs.

Results: Cutaneous lesions ranged from track marks to severe ulcerations and scarring. Mucosal lesions also took a toll on several patients. The patients had varying degrees of anxiety, depression, and mental stress.

Conclusions: Injecting Drug Abusers are prone to acquire skin diseases due to injury caused by drugs as well as by drug practices adopted and the degree of neglect may worsen these conditions. These cutaneous lesions hamper QoL and cause psychosocial disturbances.
Introduction

The WHO defines Drug abuse/Substance abuse as harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs. Psychoactive substances are the pharmacological agents that alter the behavioral, cognitive, and physiological changes in the body that, on repeated use, lead to a phenomenon referred to as dependence syndrome. This includes a strong desire for the drug, impulse, and repeated use despite harmful effects. A high priority is given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. No part of the world is free of drug abuse in the current times [1]. The advent of globalization has led to several variations in the culture and economic backgrounds in Indian population. Alongside positive implications, certain social drawbacks like substance abuse are an important measure to be taken care of. Several criminal acts and antisocial behaviors have been associated with drug abuse [2]. Several steps and special task forces are being generated by the Indian government at both the national and state level. Despite all the measures taken by the government and society, drug abuse is one of the leading causes of crime in India. India is surrounded by the world’s leading illicit drug-producing countries namely Thailand, Laos, and Myanmar constituting the golden triangle on the eastern side. Similarly, Afghanistan, Iraq, and Pakistan which constitute the golden crescent are located on the western borders of the nation. Thereby the incidence of substance abuse is on the rise especially in states like Punjab which is in close geographic contact with the above-mentioned western border [3]. Drug abuse has several implications on human health and society. These include a weak immune system, increasing rates of malnutrition, and related disorders due to neglect, weight, and appetite loss. The toxicity of these drugs can lead to several hepatic and heart diseases. Neuronal damage may result in behavioural and cognitive disorders [4].

Besides involving these systems, substance abuse can lead to several cutaneous manifestations as well which could be either due to direct injury by the offending drug or the practices of drug usage can cause secondary damage to the skin structure or even a presentation of medical complication due to drug abuse visible on the skin [5]. The early recognition of these signs is of utmost importance to prevent long-term complications like necrosis. To ease the understanding, we have tried to classify the presentations.

Classification of Skin Manifestations:

1. Injection-related effects: most commonly encountered lesions in Injecting Drug Users (IDU) are the track marks mostly seen on the arms and especially over the antecubital fold [6]. These represent the sclerosed vessels resulting from localized thrombophlebitis due to an irritant drug being abused and extravasated. The dark color at the site is due to the post-inflammatory hyperpigmentary changes occurring in the skin with an underlying affected vessel.

Skin popping: Administering drugs into the skin may result in deep punched out ulcers which heal with atrophy. These ulcers usually get secondarily affected to form large ulcers which heal slowly [7].

2. Infections: skin and soft tissue infections are common in IDUs due to their injection practices and weakened immune systems. Staphylococcus aureus and streptococcal species which are normal commensals over skin enter the deeper tissues resulting in abscesses and cellulitis [8]. Moreover there are several impurities and adulterants in drugs that have deleterious effects on skin structures. Several uncommon pathogens such as Clostridial and Eiknella which reside in the oral cavity can result in superficial and deep-seated abscesses. Wound botulism, necrotizing fasciitis and tetanus can occur due to clostridial toxins usually in the skin poppers in whom inoculation of bacilli occurs in relatively anaerobic conditions such as skin which favors their growth and toxin production [9,10]. Use of nonsterile needles poses certain threats of various viral infections including Human immunodeficiency virus (HIV) and Hepatitis B and C viruses [11]. These infections can have various skin manifestations ranging from acute maculopapular rash to chronic skin diseases [12,13].

3. Vascular complications: repeated trauma to the veins leads to vessel wall changes causing thrombophlebitis and venous thrombosis. This leads to venous incompetence and ulcerations may ensue. Furthermore, lymphatic drainage may get compromised due to lymphatic damage deteriorating the picture and leading to chronic edema of the limb [14].

Accidental intra-arterial injections may result in ischemic changes due to drugs or adulterants. Some of the drugs such as cocaine are vasoconstrictors that can result in vasospasms and compromising the blood supply to a unit resulting in its necrosis. Drug-induced vasospasm and thrombosis may result in acute pain and burning sensation in the limb and further leading to edema and cyanosis. Scrotal necrosis is seen in pudendal artery thrombosis [15]. There are reports of penile ulceration following drug administered into dorsal penile vein [16]. Intravenous abuse of cocaine may result in secondary Raynaud phenomenon and digital ulcerations and infarction in organs like the liver and kidney.
Pseudoaneurysms and mycotic aneurysms can develop following vascular injuries and infections may develop in the vessel walls. A pulsatile or non-pulsatile mass may be seen in the distribution of a vessel which may be wrongfully considered as an abscess and if incised may result in fatal outcomes [17]. These aneurysms are generally infected by bacteria such as staphylococcus and streptococcus species. In some instances, Candida albicans may be the infectious agent [18].

Objectives

Primary Objective
1. To study the clinical-epidemiological profile of the skin diseases in IDUs attending Oral Substitution Therapy (OST) center in Northern India.

Secondary Objectives
1. To assess the socio-demographic profile of IDUs.
2. To assess the psychological impact of skin conditions in IDUs attending oral substitution therapy center.
3. To assess the quality of life (QoL) of IDUs attending oral substitution therapy center.

Methods

A total of 100 IDUs visiting the OST center at the Government Medical College, Amritsar, in Northern India who met the inclusion criteria were randomly enrolled in the study. Inclusion criteria:

1. IDUs of both sex and aged more than 18 years.
2. IDUs visiting OST centers who gave consent for the study.

Exclusion criteria:

1. IDUs of drug abuse employing routes other than intravenous.
2. IDUs not giving consent for the study.
3. IDUs with other primary dermatoses.
4. IDUs with organic mental disorders or known significant medical conditions.

After signing written informed consent, a brief history regarding their drug abuse – duration, type of drug, and route of administration was enquired from patients. History of any skin disease before IDU abuse was asked. A thorough clinical examination was done after full body exposure. Bed-side tests for skin diseases if required were done. Lesions were examined clinically and with dermoscope as well.

Questionnaires regarding the Dermatological QoL Index (DLQI) were filled to know about the impact of skin conditions. Secondly, the Depression, Anxiety, Stress Scale (DASS) questionnaire for assessing the psychological status of patients on de-addiction therapy was filled. Thirdly, a WHO QoL index questionnaire was used to look into the overall QoL of these patients visiting the OST center. At last, the results were tabulated and statistically analyzed.

Results

In our study, we observed that the mean age of the IDUs was 30.08 with a majority in the age group of 21-30 years. Among the study group, 98 were males and 2 were females. Laborers accounted for the majority being 33% and 17 were drivers; the rest of the IDUs had several other professions. All the IDUs had heroin abuse while 8 had concomitant cocaine and 3 had cannabis addiction as well. The mean duration of drug abuse among the IDUs was 8.34 years while the maximum duration of injectables observed for the past was 1 to 5 years. In the study group, the last dose of the abused drug taken was less than one month in 76% while others had a lapse time of more than 1 month. Among the IDUs, 99 were being managed with buprenorphine and naloxone combination sublingual tablets and one was being given oral methadone. The literacy rate varied from 12/100 being illiterate to 8/100 being graduate (with a graduation degree in any field) and the rest had education level between primary to senior secondary education. Thirty-eight patients had income less than 10,000, 50 had 10,000 to 20,000 and 12 had more than 20,000 Indian rupees. Fifty-two IDUs were unmarried, 46 were married and 2 were divorced. A history of smoking was present in 57/100, while 82/100 were alcoholics. Of the 100 IDUs, 80 were positive for hepatitis C virus (HCV) infection, 10 had HIV infection and among them, 9 had concomitant HCV and HIV positivity. One among them had type 1 insulin-dependent diabetes mellitus, 1 was hypertensive, 1 had chronic kidney disease (Tables 1 and 2).

In the study group, 84 patients had black-colored spots and scars over their body, 34 reported a history of chronic itching and 6 had ulcers over various body parts. The duration of these complaints ranged from few months to several years. These lesions were clustered around upper limbs in 88% of all followed by 8% over lower limbs and 4% over the other body parts. Eight patients had a history of concomitant joint pains. Among these patients, 38% received topical or oral treatment. The commonly used topical agent was clobetasol cream and an oral agent was an antihistamine. Seven patients were on Highly Active Anti Retro Viral Therapy (HAART) and 2 were taking Anti Hepatitis C therapy (lepidasvir and sofosbuvir).

On examination, 92 patients had track marks, 54 had hesitation marks, 53 had tattoos while small round atrophic scars were present in all the patients. Scabies was the most
Table 1. Socio-Demographic Profile of the injecting drug users visiting Oral Substitution Therapy centers.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>N. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>21-30</td>
<td>53</td>
<td>53.0%</td>
</tr>
<tr>
<td>31-40</td>
<td>38</td>
<td>38.0%</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>5</td>
<td>5.0%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Male</td>
<td>98</td>
<td>98.0%</td>
</tr>
<tr>
<td>Address (Rural/Urban)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>21</td>
<td>21.0%</td>
</tr>
<tr>
<td>Urban</td>
<td>79</td>
<td>79.0%</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Married</td>
<td>46</td>
<td>46.0%</td>
</tr>
<tr>
<td>Unmarried</td>
<td>52</td>
<td>52.0%</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diploma</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Elementary</td>
<td>18</td>
<td>18.0%</td>
</tr>
<tr>
<td>Graduate</td>
<td>8</td>
<td>8.0%</td>
</tr>
<tr>
<td>Illiterate</td>
<td>12</td>
<td>12.0%</td>
</tr>
<tr>
<td>Matriculation</td>
<td>23</td>
<td>23.0%</td>
</tr>
<tr>
<td>Primary</td>
<td>24</td>
<td>24.0%</td>
</tr>
<tr>
<td>Senior Secondary (post matriculation)</td>
<td></td>
<td>13.0%</td>
</tr>
<tr>
<td>Income (in Rupee)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5000</td>
<td>11</td>
<td>11.0%</td>
</tr>
<tr>
<td>5000-10000</td>
<td>27</td>
<td>27.0%</td>
</tr>
<tr>
<td>&gt; 10000</td>
<td>62</td>
<td>62.0%</td>
</tr>
<tr>
<td>Drug Abused</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine and heroin</td>
<td>8</td>
<td>8.0%</td>
</tr>
<tr>
<td>Heroin</td>
<td>89</td>
<td>89.0%</td>
</tr>
<tr>
<td>Heroin and cannabis</td>
<td>3</td>
<td>3.0%</td>
</tr>
<tr>
<td>Duration of abuse (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5.0</td>
<td>29</td>
<td>29.0%</td>
</tr>
<tr>
<td>6-10.0</td>
<td>47</td>
<td>47.0%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>24</td>
<td>24.0%</td>
</tr>
<tr>
<td>Treatment given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>99</td>
<td>99.0%</td>
</tr>
<tr>
<td>Methadone</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>43</td>
<td>43.0%</td>
</tr>
<tr>
<td>Present</td>
<td>57</td>
<td>57.0%</td>
</tr>
</tbody>
</table>

Table 2. Chronic conditions and co-morbidities in injecting drug users.

<table>
<thead>
<tr>
<th>Past Illness</th>
<th>N of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Hip joint surgery</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Type-1 diabetes</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>None</td>
<td>94</td>
<td>94.0%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>99</td>
<td>99.0%</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>99</td>
<td>99.0%</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>90</td>
<td>90.0%</td>
</tr>
<tr>
<td>Positive</td>
<td>10</td>
<td>10.0%</td>
</tr>
<tr>
<td>HBsAg</td>
<td>No. of cases</td>
<td>Percentage</td>
</tr>
<tr>
<td>Negative</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>20.0%</td>
</tr>
<tr>
<td>HCV</td>
<td>No. of cases</td>
<td>Percentage</td>
</tr>
<tr>
<td>Negative</td>
<td>80</td>
<td>80.0%</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

common skin disease affecting 23 patients of which nine had nodular lesions as well. Superficial dermatophytosis was seen in 12 patients. Six patients had facial melanosis, 4 had intertrigo, 2 had acne vulgaris and 2 had balanitis. Other skin and soft tissue ailments present were hyperhidrosis, urticaria, thrombophlebitis, acneiform eruptions, verrucae, and genital herpes (Table 3).

Angular cheilitis was seen in 2 patients, 45 had pigmentation over lips and seven had depigmented patches over the lips. Examination of buccal mucosa revealed bluish-black pigmentation in 77 patients and erosions in five ones. Dirty yellowish-brown staining over teeth was present in 69 patients and 2 had dental caries. On examination of the ginvigival sulcus, 33 had pigmentary changes, 24 had Sub Mucosal Fibrosis, 8 had leukoplaikia and 3 had cobblestone mucosa.

Hair examination revealed trichomycosis in 2 patients, generalized sparsity in 2 subjects, and androgenetic alopecia in 1. Longitudinal melanonychia was the most common nail abnormality observed seen in 29 IDUs. A brownish discolored nail plate was seen in 4 IDUs, 3 ones had dystrophic nails, 2 had koilonychia and 1 had paronychia (Table 4).
Table 3. Skin conditions encountered in injecting drug users.

<table>
<thead>
<tr>
<th>Skin Lesions Description</th>
<th>N of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Track Marks</td>
<td>92</td>
<td>92.0%</td>
</tr>
<tr>
<td>Atrophic Scars</td>
<td>100</td>
<td>100.0%</td>
</tr>
<tr>
<td>Hesitation Marks</td>
<td>54</td>
<td>54.0%</td>
</tr>
<tr>
<td>Tattoos</td>
<td>53</td>
<td>53.0%</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne vulgaris</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Acneiform eruptions, intertrigo</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Atrophic scars in groins and nodular scabies</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Balanitis</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Extensive Tinea corporis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Facial melanosis</td>
<td>5</td>
<td>5.0%</td>
</tr>
<tr>
<td>Folliculitis, scabies</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Herpes genitalis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Hyperhidrosis, tightness of skin</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Intertrigo</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Intertrigo, facial melanosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Large atrophic scars on bilateral thighs</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Mottled pigmentation and hyperkeratosis on palms</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Post herpetic zosteriform scars</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Scabies</td>
<td>11</td>
<td>11.0%</td>
</tr>
<tr>
<td>Scabies and acne corporis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Scabies nodular</td>
<td>8</td>
<td>8.0%</td>
</tr>
<tr>
<td>Scars in groin and pubic region</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sebaceous cysts scrotum</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Seborrheic keratosis and facial melanosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Soft tissue swelling</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tinea corporis Cruris and facial melanosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tinea corporis Cruris and ulcer on right palm, soft tissue</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tinea corp., scabies with folliculitis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tinea corporis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tinea corporis with ulcers</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tineacruris</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Tineacruris, facial melanosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Trichomycosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ulcer non-healing on left leg</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ulcer on arm</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ulcer over hand and facial melanosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ulcers on left forearm</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ulcers on thighs, hands and feet, xanthelasmapalpebrum</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Warts on hands</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>None</td>
<td>37</td>
<td>37.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Table 4. Oral and skin appendageal conditions seen in injecting drug users.

<table>
<thead>
<tr>
<th>Mucosal Lesions_Lips</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angular cheilitis</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Depigmented patches</td>
<td>7</td>
<td>7.0%</td>
</tr>
<tr>
<td>Discoloration</td>
<td>45</td>
<td>45.0%</td>
</tr>
<tr>
<td>None</td>
<td>46</td>
<td>46.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buccal mucosa lesions</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>77</td>
<td>77.0%</td>
</tr>
<tr>
<td>None</td>
<td>22</td>
<td>22.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucosal Lesions_Teeth</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caries</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Stained</td>
<td>69</td>
<td>69.0%</td>
</tr>
<tr>
<td>None</td>
<td>29</td>
<td>29.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucosal Lesions_Gingivolabial Sulcus</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobblestoning</td>
<td>3</td>
<td>3.0%</td>
</tr>
<tr>
<td>Erosions</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Gingival ulcer, SMF and pigmentation</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Gum recession with gingival erosion and leukoplakia</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>7</td>
<td>7.0%</td>
</tr>
<tr>
<td>Micro erosions over labial mucosa, recession of gums</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>33</td>
<td>33.0%</td>
</tr>
<tr>
<td>Pigmentation, SMF</td>
<td>24</td>
<td>24.0%</td>
</tr>
<tr>
<td>SMF</td>
<td>6</td>
<td>6.0%</td>
</tr>
<tr>
<td>None</td>
<td>23</td>
<td>23.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hair</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgenetic alopecia</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sparsity</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Trichomycosis</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>None</td>
<td>95</td>
<td>95.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nails</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clubbing</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Discolored</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>Dystrophic nail</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>Leukonychia</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Long. Melanonychia</td>
<td>29</td>
<td>29.0%</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>Paronychia, longitudinal Melanonychia</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>None</td>
<td>59</td>
<td>59.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

SMF = submucosal fibrosis
Conclusions

Drug abuse has been taking a great toll on the health and well-being of the community for the past few decades. A rise in injecting drug abuse has been posing threat to the individual health and thus to QoL. Skin is among the neglected organs among IDUs and the tendency of neglect increases with the duration of abuse [19]. Track marks are linear or

Table 5. Psychological aspects and quality of life Parameters of injecting drug users.

<table>
<thead>
<tr>
<th>DLQI Score (Dermatology Life Quality Index)</th>
<th>N of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1.0</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>2-5.0</td>
<td>26</td>
<td>26.0%</td>
</tr>
<tr>
<td>6-10.0</td>
<td>54</td>
<td>54.0%</td>
</tr>
<tr>
<td>11-20.0</td>
<td>20</td>
<td>20.0%</td>
</tr>
<tr>
<td>21-30.0</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Depression</th>
<th>N of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>90.0%</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>5.0%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3.0%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.0%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>N of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84</td>
<td>84.0%</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>9.0%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2.0%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stress</th>
<th>N of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73</td>
<td>73.0%</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>13.0%</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>9.0%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3.0%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WHO-QOL</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>100</td>
<td>19.00</td>
<td>60.00</td>
<td>30.08</td>
<td>6.53</td>
</tr>
<tr>
<td>Duration of Abuse (Years)</td>
<td>100</td>
<td>2.00</td>
<td>18.00</td>
<td>8.34</td>
<td>3.77</td>
</tr>
<tr>
<td>DLQI Score</td>
<td>100</td>
<td>2.00</td>
<td>18.00</td>
<td>7.88</td>
<td>3.28</td>
</tr>
<tr>
<td>WHO - QOL (BREF) Domain 1</td>
<td>100</td>
<td>38.00</td>
<td>50.00</td>
<td>42.92</td>
<td>3.75</td>
</tr>
<tr>
<td>WHO - QOL (BREF) Domain 2</td>
<td>100</td>
<td>31.00</td>
<td>44.00</td>
<td>34.35</td>
<td>4.92</td>
</tr>
<tr>
<td>WHO - QOL (BREF) Domain 3</td>
<td>100</td>
<td>31.00</td>
<td>44.00</td>
<td>37.50</td>
<td>3.89</td>
</tr>
<tr>
<td>WHO - QOL (BREF) Domain 4</td>
<td>100</td>
<td>31.00</td>
<td>44.00</td>
<td>37.50</td>
<td>3.89</td>
</tr>
</tbody>
</table>

DLQI revealed moderate effect (score 6-10) on QoL due to skin affection in 54% of patients, followed by mild effect (score 2-5) in 26% and very large effect (score 11-20) in 20 patients. Depression Anxiety Stress Score revealed extremely severe depression in 1, severe in 1, moderate in 3, and mild depression in 1 IDU. Anxiety observed was extreme in 1, severe in 2, moderate in 4, and mild in 9. The stress index showed extreme stress in 2, severe in 3, moderate in 9, and mild in 13.

WHOQ-OL questionnaire was used which gave a mean of 42.92, 34.35, 47.06, 37.50, with a standard deviation (SD) of 3.75, 4.92, 11.69, and 3.89 in Domain 1, 2, 3, and 4, respectively (Table 5).
closely spaced needle pricks seen as black dots on the skin overlying veins in IDUs. (Figure 1). These are among the most common and absolute signs seen in active IDUs. There can be surrounding erythema or induration which depicts inflammatory reaction either due to extravasated drug or infection in the intradermal or subcutaneous tissue. Thrombophlebitis can be associated with track marks at times and can lead to cellulitis if not taken care of. On dermoscopic examination, these are seen as black dots or hemorrhages, comedones-like or plug arranged linearly with bluish-black to the erythematous background (Figure 2). Small rounded atrophic scars are another hallmark of injecting drug abuse. These are a result of skin popping that form small ulcers which heal with atrophy. In patients with the tendency to keloid formation, large nodular lesions may be seen instead of atrophic scars.

Among the infections and infestations, scabies was the most common disease encountered and the level of neglect further poses a threat to its treatment. Poor hygiene is a significant risk factor to acquire scabies besides deranged itch-scratch cycle, relatively immune-compromised status are other contributory factors. The diagnosis of scabies may be at times missed by psychiatrists and thought to be related to drug abuse-delusion of parasitosis [20]. In such instances full body exposure and site-specific examination may reveal burrows of mite and clinches the diagnosis. Superficial dermatophytosis, a fungal infection, is another common infection encountered among IDUs which presents as round and annular itchy plaques over the body (Figure 3). Other infections include bacterial folliculitis and infected wounds.

Viral disease transmission is common among IDUs due to sharing of syringes due to which there is an increased rate

![Figure 1](image-url). (A) Multiple depressed scar marks over inguinal region. (B) Skin popping marks. (C) Hesitation marks. (D) Track marks.
of incidence of viral Hepatitis and HIV-AIDS among them [21]. In our study, the majority of the patients were positive for HCV and HIV. This draws attention to checking the behavior and actions of IDUs and adopting measures preventing them.

The oral cavity is yet another area to be stressed upon in IDUs as they tend to be smokers, alcoholics, and tobacco abusers with poor oral hygiene and the degree of neglect they have may pose drastic effects such as oral malignancies [22,23]. The changes observed in our studies included pigmentation related to nicotine and depigmented patches too can be toxic reactions to the melanocytes. The gingivolabial mucosa was the most exploited area in the oral cavity due to the habit of keeping the tobacco pouch undersurface of the lip and most patients had pigmenary changes, erosions, and submucosal fibrosis and few had leukoplakia and

Figure 2. On dermoscopic examination (100X. ILLUCO), black dots or hemorrhages, comedones like or plug arranged linearly with bluish-black and brownish to reddish white background.

Figure 3. (A) Scabies mite burrows. (B) Extensive Tinea Corporis. (C) Soft tissue swelling of arm (patient was T1 DM). (D) Herpes genitalis.
The study had several limitations like the fact that the confirmatory diagnosis of the skin disorders was not established due to short interaction between patient and doctor and unavailability of investigations at the OST center. The second bias was the neglect shown by the IDUs towards skin conditions which lead to a certain degree of concealment of skin conditions. Thirdly, many IDUs did not consent for the full body examination leading to missing some important areas of examination like genitalia and groins which are potential sites for infections and sexually transmitted infections as well as spots of drug injection. Lastly, it was not a case control study and hence statistics could not be performed; moreover, the number of study patients was limited. These limitations can be overcome by bringing together the two specialties of de-addiction and Dermatology and stressing cobble-stoning which tend to be premalignant conditions and may lead to drastic situations if not addressed accordingly (Figure 4).

In the assessment of QoL related to dermatological conditions, the dermatology QoL index has proven to be a good tool [24]. In our study, a majority of IDUs had moderately hampered life quality which means the skin conditions either due to the direct effect of drugs or secondary involvement has brought about changes in the daily routine of IDUs which can be social, psychological, or economic encroachment.

Similarly, the mental state of the patients was assessed by the Depression Anxiety Stress scale which is a crude and partially objective method of assessment of the inner horizon of patients. It revealed a significant alteration in the mental state of the IDUs.

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over the need for periodic examination of the skin of IDUs to look for any direct or indirect effects of drug abuse.

Skin conditions occurring in IDUs are a result of direct injury to the skin by the offending drug or by the methods used to introduce drug into body. Track marks resulting from repeated intravenous drug abuse are the commonest occurrence followed by atrophic rounded scars due to drug popping into the skin. Infectious conditions of the skin are common which occur either because of the contaminated drug or by the neglect of an IDU in receiving treatment. Hesitation marks seen in a large number of candidates relate well with altered mental condition of the IDUs. Drugs and altered mental state form a vicious cycle such that it almost becomes impossible for IDUs to maintain a sound conscience and psychological and physical dependence further takes its toll. Thus, dermatologists and psychologists should collaborate to address the healthcare needs of an IDU so that timely necessary actions can be taken.

References

Dermatopathological Correlation of Clinically Challenging Cutaneous Lesions: a Single Center Experience of 2184 Cases

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Key words: dermatology, dermatopathology, clinicopathological correlation, COVID-19


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Although a trained eye can easily identify typical skin lesions, histopathological examination and clinicopathological correlation are critical in challenging cases.

Objectives: The primary objective is to organize the final diagnoses reached following clinicopathological consensus in clinically challenging cutaneous lesions, identifying the most common diagnostic scenarios encountered by dermatopathologists and discussing their diverse differentials submitted by clinicians. The secondary objective is to investigate how the case profile and clinician decision-making processes evolved during the COVID-19 pandemic.

Methods: Skin and mucosa samples collected by the dermatology department between 2016 and 2020 were classified based on pathology reports. For frequent diagnoses, preliminary diagnoses stated by clinicians on pathology requisition forms were reviewed. The years preceding and following the first nationally reported COVID-19 case were compared to investigate the pandemic's impact on the distribution of dermatology and dermatopathology cases.

Results: One thousand nine hundred and eighty-nine reports were classified into 4 major categories: inflammatory (49.8%), neoplastic (30.1%), other diseases (7.1%), and non-diagnostic (12.8%). We further classified inflammatory diseases based on major tissue reaction patterns and neoplasms based on cell origin. We analyzed the leading diagnoses in each category, discussed their differential
Introduction

A trained eye is essential in the identification of skin diseases, yet even common dermatoses can manifest with perplexing lesions [1]. Moreover, a newly formed or regressed rash may not exhibit the classic morphological features [2]. Patients may further complicate the problem by scratching and irritating their lesions, or by self-treating with exogenous and endogenous substances [2]. A skin biopsy is one of the most effective methods for reaching a diagnosis in challenging cases [3].

Histopathological examination, on the other hand, has a different set of limitations to consider. Inadequate sampling, biopsy of an inappropriate location or performing the biopsy at an early or late stage, can result in limited findings [4]. Even with an adequate sample, histopathological examination alone may be insufficient to make a definitive diagnosis and may occasionally reveal findings that contradict clinical information [4]. Another major issue is the clinician’s failure to provide sufficient information about the patient or a breakdown in communication between the two departments [5]. A successful final diagnosis is better achieved by linking the clues through clinicopathological correlation [6].

A biopsy requisition form is filled out to transfer the clinical information needed by the pathologist to correctly interpret the histopathological examination [7]. A properly completed form will improve communication between the clinician and the pathologist, allowing for a more accurate diagnosis [6]. Retrospective studies on the consistency of clinical information and pathology results report complete concordance in only 28.3%-68.0 % of cases [3,8–11]. Although these studies emphasize the importance of clinicopathological correlation, they do not provide guidance about the diagnostic dilemmas frequently encountered by dermatologists and dermatopathologists in real-life scenarios.

In this study, we classified the frequently encountered challenging cases and their diagnoses after clinicopathological correlation. All cases were evaluated and concluded on a case-by-case basis in weekly meetings with a dermatologist and a dermatopathologist. We also used clinical information from pathology requisition forms to determine the most frequently considered alternative diagnoses by clinicians prior to biopsy. Finally, we investigated how the COVID-19 pandemic affected dermatology and dermatopathology practice and case distribution.

Objectives

• Organizing the final diagnoses reached after clinicopathological consensus in clinically challenging dermatology cases.
• Identifying and discussing the alternative diagnoses that are more likely to be considered by clinicians prior to biopsy, and providing clues for dermatologists to reduce error in practice.
• Investigating the effects of the pandemic on the case profile of dermatology and dermatopathology departments following the first nationally reported COVID-19 case.

Methods

This research was conducted in a referral hospital, serving around half a million people annually. We classified the pathology reports of skin and mucosa samples collected by the dermatology department between 2016 and 2020. All reports indicating a definitive diagnosis were classified under inflammatory, neoplastic, or other diseases. Reports that lacked a diagnosis or a useful clue were categorized as non-diagnostic. Samples that were insufficient or obtained for direct immunofluorescence investigations were excluded.

We further classified inflammatory diseases into six categories based on major tissue reaction patterns, and neoplastic diseases into three categories based on cell origin. The remaining reports diagnosed a wide range of diseases and they were classified as “Other”. Reports demonstrating a specific inflammatory pattern without a definitive diagnosis were still considered useful to clinicians and classified under that specific pattern as non-diagnostic (eg, granulomatous pattern, non-diagnostic) (Figure 1).

The three most frequently reported diagnoses by pathologists in each category were compiled. In addition, for each diagnosis, we listed the three most common differential diagnoses submitted by clinicians prior to biopsy.

All comparisons examining the effects of the pandemic were made in the years preceding and following the first nationally reported COVID-19 case. We

Conclusions: We presented and discussed the frequently encountered confounding cases to sketch the diagnostic landscape. In the authors’ experience, clinicopathological correlation can increase the rate of reaching the diagnosis by up to 75.3%.
compared the case profiles reached after clinicopathological consensus using the same classification method. We also compared how frequently we biopsied the patients

\[
\left( \frac{\text{Number of biopsies taken}}{\text{Total number of clinical examinations}} \times 100 \right)
\]

, and the percentage of dermatology department samples sent in

\[
\left( \frac{\text{Number of dermatology samples}}{\text{Total samples received by pathology}} \times 100 \right)
\]

. Next, as an indicator of case diversity, we compared the number of different definitive diagnoses made. Finally, in order to determine the distribution of cases presented in the dermatology outpatient department, we classified the registered ICD-10 codes.

SPSS v.26 was used for statistical analysis. The Chi-square test for proportions or the Fishers’ exact test was used, when appropriate. Statistical significance was determined by p values less than 0.05.

### Results

In the majority of categories, pathological diagnosis matched the most frequently submitted differential diagnosis by clinicians. The second and third differentials were the most difficult to distinguish clinically. As a result, they were more frequently proposed as alternate diagnoses to pathologists.

Inflammatory diseases accounted for 49.8% of all reports (Table 1 and Table 2). Looking at the subcategories, we discovered that granulomatous diseases accounted for 3.9% of all cases, psoriasiform diseases 11.1%, lichenoid diseases

![Figure 1](image-url). The categorization of pathology reports and the number of cases in each category.
Table 1. Granulomatous, psoriasiform, and lichenoid diseases. The pathologist’s diagnosis and the three most frequently submitted clinical differential diagnoses prior to biopsy

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Pathologist’s Diagnosis</th>
<th>Clinician’s Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Granulomatous Diseases</td>
<td></td>
</tr>
</tbody>
</table>
| 15              | 1- Granulomatous pattern, non-diagnostic | 1- Sarcoidosis  
2- Kaposi’s sarcoma  
3- Mycobacterial infection (tuberculosis, leprosy, etc.) |
| 13              | 2- Granuloma annulare | 1- Granuloma annulare  
2- Erythema annulare centrifugum  
3- Sarcoidosis |
| 7               | 3- Sarcoidosis | 1- Sarcoidosis  
2- Cutaneous lymphoma  
3- Pseudolymphoma |
|                 | Psoriasiform Diseases  |                                    |
| 92              | 1- Psoriasis vulgaris and subtypes | 1- Psoriasis vulgaris and other subtypes  
2- Lichen planus and variants  
3- Contact dermatitis |
| 40              | 2- Psoriasiform pattern, non-diagnostic | 1- Psoriasis vulgaris and other subtypes  
2- Contact dermatitis  
3- Pityriasis rubra pilaris |
| 30              | 3- Parapsoriasis | 1- Parapsoriasis  
2- Mycosis fungoides  
3- Nummular dermatitis |
|                 | Lichenoid Diseases     |                                    |
| 71              | 1- Lichen planus | 1- Lichen planus and variants  
2- Contact dermatitis  
3- Lichenoid drug eruption |
| 47              | 2- Lichenoid pattern, non-diagnostic | 1- Lichen planus  
2- Contact dermatitis  
3- Drug eruption |
| 21              | 3- Pigmented purpuric dermatosis | 1- Pigmented purpuric dermatosis  
2- Mycosis fungoides  
3- Contact dermatitis |

Table 2. Vasculopathic, spongiotic, and vesiculobullous diseases. The pathologist’s diagnosis and the three most frequently submitted clinical differential diagnoses prior to biopsy

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Pathologist’s Diagnosis</th>
<th>Clinician’s Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vasculopathic Diseases</td>
<td></td>
</tr>
</tbody>
</table>
| 47              | 1- Leukocytoclastic vasculitis | 1- Cutaneous small-vessel vasculitis  
2- IgA vasculitis  
3- Pigmented purpuric dermatosis |
| 23              | 2- Ulcers of various causes | 1- Squamous cell carcinoma  
2- Pyoderma gangrenosum  
3- Perforating dermatoses |
| 12              | 3- IgA vasculitis | 1- IgA vasculitis  
2- Leukocytoclastic vasculitis  
3- Not available |
|                 | Spongiotic Diseases     |                                    |
| 102             | 1- Spongiotic pattern, non-diagnostic | 1- Mycosis fungoides  
2- Parapsoriasis  
3- Psoriasis vulgaris and other subtypes |

Table 2 continues
<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Pathologist’s Diagnosis</th>
<th>Clinician’s Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>2- Contact dermatitis</td>
<td>1- Contact dermatitis</td>
</tr>
<tr>
<td></td>
<td>2- Psoriasis vulgaris and other subtypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3- Mycosis fungoides</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>3-Pityriasis rosea</td>
<td>1- Pityriasis rosea</td>
</tr>
<tr>
<td></td>
<td>2- Psoriasis vulgaris and other subtypes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3- Erythema annulare centrifugum</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>1-Bullous pemphigoid</td>
<td>1- Bullous pemphigoid</td>
</tr>
<tr>
<td></td>
<td>2- Pemphigus vulgaris</td>
<td>2- Pemphigus vulgaris</td>
</tr>
<tr>
<td></td>
<td>3- Dermatitis herpetiformis</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2-Vesiculobulous pattern, non-diagnostic</td>
<td>1- Bullous pemphigoid</td>
</tr>
<tr>
<td></td>
<td>2- Pemphigus vulgaris</td>
<td>2- Pemphigus vulgaris</td>
</tr>
<tr>
<td></td>
<td>3- Allergic contact dermatitis</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3-Pemphigus vulgaris</td>
<td>1- Pemphigus vulgaris</td>
</tr>
<tr>
<td></td>
<td>2- Bullous pemphigoid</td>
<td>2- Bullous pemphigoid</td>
</tr>
<tr>
<td></td>
<td>3- Pemphigus foliaceus</td>
<td></td>
</tr>
</tbody>
</table>

Vesiculobullous Diseases

12.8%, vasculopathic diseases 5.1%, spongiotic diseases 15.4%, and vesiculobullous diseases 3.1%.

Reports describing clues that point to a specific inflammatory pattern but do not provide a definitive diagnosis were among the top three in each category. This category was only replaced by ulcers of various causes in the vasculopathic reaction pattern. The ratio of these reports was found to be 0.7% for granulomatous diseases, 2% for psoriasiform diseases, 2.3% for lichenoid diseases, 1.1% for vasculopathic diseases, 5.1% for spongiotic diseases, and 0.5% for vesiculobullous diseases.

In 30.1% of all reports, a definitive diagnosis of neoplasia was made. Keratinocytic neoplasms accounted for 11.2%, melanocytic neoplasms 7.1%, and other cell-derived neoplasms 11.7% of all reports. Basal cell carcinoma, squamous cell carcinoma, malignant melanoma, and mycosis fungoides were the most common malignant neoplasms reported (Table 3).

Other diseases accounted for 7.1% of total reports after excluding inflammatory and neoplastic diseases. Clinicians needed assistance distinguishing morphea from extragenital lichen sclerosus and mycosis fungoides, verrucas from verrucous carcinoma and squamous cell carcinoma, and dermatophytes from erythema annulare centrifugum and psoriasis in this category (Table 4).

In total, 12.8% of all reports were unhelpful in terms of providing any diagnostic findings. The percentage of reports that provided a single definitive diagnosis was 75.3%. Finally, 11.9% of reports contained diagnostic hints but did not provide a definitive diagnosis.

Following a year of pandemic, the number of reports in each category dropped dramatically. The percentage of cases with spongiotic patterns has decreased, while the percentage of cases with keratinocytic and melanocytic neoplasms has increased (Table 5).

The number of biopsies taken per 100 dermatological examinations was reduced from 2.7 to 2.1. Furthermore, the percentage of skin and mucosa samples received by pathology was reduced from 6.9 percent to 2.7 percent. The case diversity was also reduced from 113 to 60 distinct definitive diagnoses.

Following the first nationally documented COVID-19 case, the number of admissions to the dermatology outpatient department decreased from 16,511 to 5,550 annually. For these admissions, the examining dermatologists registered a total of 21,820 and 6,953 ICD-10 codes, respectively. The total number of diagnoses has decreased in every category except vesiculobullous diseases, where the admission count was the same (81 per year). The incidence of eczematous (including contact, atopic, seborrheic, and nummular dermatitis, among others), infectious (viral, bacterial, fungal, and parasitic), and vesiculobullous diseases (pemphigus and pemphigoid diseases), as well as urticaria & angioedema, and drug-related eruptions, increased significantly. Adnexal diseases (acne, rosacea, hidradenitis suppurativa, hyperhydrosis), papulosquamous diseases (psoriasis, pityriasis rubra pilaris, pityriasis rosea), pigmentation disorders (vitiligo, melasma, post-inflammatory hyperpigmentation among others), and benign neoplasms (seborrheic keratosis, melanocytic nevi, various cyts, etc) all had a significant decrease in incidence (Figure 2).

Conclusions

The majority of diagnostic traffic between dermatology and pathology is driven by inflammatory (49.8%) and neoplastic (30.1%) diseases. The remaining diseases accounted for 7.1% of all reports and covered a broad diagnostic range that could not be classified in either of these two major
### Table 3. Neoplasms of keratinocytic, melanocytic, and other cell origins. The pathologist’s diagnosis and the three most frequently submitted clinical differential diagnoses prior to biopsy

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Pathologist’s Diagnosis</th>
<th>Clinician’s Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keratinocytic Neoplasm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>1-Basal cell carcinoma</td>
<td>1- Basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Bowen's disease</td>
</tr>
<tr>
<td>57</td>
<td>2-Squamous cell carcinoma</td>
<td>1- Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Actinic keratosis</td>
</tr>
<tr>
<td>38</td>
<td>3-Actinic keratosis</td>
<td>1- Actinic keratosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Basal cell carcinoma</td>
</tr>
<tr>
<td><strong>Melanocytic Neoplasm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>1-Melanocytic nevus</td>
<td>1- Melanocytic nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Atypical melanocytic nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Malignant melanoma</td>
</tr>
<tr>
<td>8</td>
<td>2-Dysplastic nevus</td>
<td>1- Atypical melanocytic nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Melanocytic nevus</td>
</tr>
<tr>
<td>5</td>
<td>3-Malignant melanoma</td>
<td>1- Malignant melanoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Atypical melanocytic nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Squamous cell carcinoma</td>
</tr>
<tr>
<td><strong>Neoplasms Caused by Other Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>1-Acrochordon</td>
<td>1- Acrochordon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Melanocytic nevus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Not available</td>
</tr>
<tr>
<td>31</td>
<td>2- Various cysts</td>
<td>1- Epidermoid cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Trichilemmal cyst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Syringoma</td>
</tr>
<tr>
<td>23</td>
<td>3-Mycosis fungoides</td>
<td>1- Mycosis fungoides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Parapsoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Contact dermatitis</td>
</tr>
</tbody>
</table>

### Table 4. The other diseases, excluding inflammatory and neoplastic. The pathologist’s diagnosis and the three most frequently submitted clinical differential diagnoses prior to biopsy

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Pathologist’s Diagnosis</th>
<th>Clinician’s Differential Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>1- Morphea</td>
<td>1- Morphea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Lichen sclerosus (extragenital)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Mycosis fungoides</td>
</tr>
<tr>
<td>25</td>
<td>2- Verruca vulgaris</td>
<td>1- Verruca vulgaris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Verrucous carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Squamous cell carcinoma</td>
</tr>
<tr>
<td>19</td>
<td>3- Dermatophytosis</td>
<td>1- Tinea incognito</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- Erythema annulare centrifugum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3- Psoriasis vulgaris and other subtypes</td>
</tr>
</tbody>
</table>

categories. In total, 75.3% of cases had a definitive diagnosis after clinicopathological correlation, while 11.9% of cases only had diagnostic clues. Finally, 12.8% of reports yielded no diagnostic information.

In granulomatous diseases, cutaneous sarcoidosis is a frequently investigated diagnosis by both clinicians and pathologists, and it has a wide range of clinical manifestations, some more specific than others [12]. Although histopathological features are invaluable, it should be kept in mind that classical naked granulomas will not always be encountered [13,14]. Clinically suggestive findings include the disappearance of background erythema with diascopy,
drugs, metals, foodstuffs, or systemic diseases), particularly in the oral mucosa [17]. Although difficult, establishing a link between exposure and disease, as well as the resolution of lesions when the offending agent is removed, is strongly suggestive, but the regression period may take months [17]. The same holds true for lichenoid skin reactions [18]. Lichenoid skin reactions are characterized by larger, eczematous papules, sometimes with a psoriasiform morphology, and Wickham's striae may be absent [18]. Eczematizing lesions can become widespread, resulting in increased desquamation [18]. It can manifest as a symmetrical (often photo-distributed) eruption on the trunk and extremities, with a tendency to leave post-inflammatory hyperpigmentation [18]. Follicular involvement revealing an apple-jelly color [15], and the appearance of orange-yellow structureless areas in a focal or diffuse pattern with dermatoscopy [16]. In dermatoscopy, vascular structures may appear as linear or branching vessels, rarely dotted or glomerular. Other less common dermatoscopic findings include dilated follicles, follicular plugs, yellow-white scales, milia-like cysts, white structureless areas and crystalline structures [16].

Lichen planus and its variants can have overlapping clinical presentations with diseases such as psoriasis, contact dermatitis, and lichenoid drug reactions. Clinical and histopathological findings may be insufficient to differentiate between lichenoid diseases and lichenoid reactions (caused by drugs, metals, foodstuffs, or systemic diseases), particularly in the oral mucosa [17]. Although difficult, establishing a link between exposure and disease, as well as the resolution of lesions when the offending agent is removed, is strongly suggestive, but the regression period may take months [17]. The same holds true for lichenoid skin reactions [18]. Lichenoid skin reactions are characterized by larger, eczematous papules, sometimes with a psoriasiform morphology, and Wickham's striae may be absent [18]. Eczematizing lesions can become widespread, resulting in increased desquamation [18]. It can manifest as a symmetrical (often photo-distributed) eruption on the trunk and extremities, with a tendency to leave post-inflammatory hyperpigmentation [18]. Follicular involvement

| Table 5. Classification of diagnoses reached after clinicopathological consensus in the years preceding (2019) and following (2020) the first nationally reported COVID-19 case |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | 2019, N (%)     | 2020, N (%)     | Difference (%)  | P (Two-tailed)  |
| **Inflammatory Diseases**       |                 |                 |                 |                 |
| Granulomatous                   | 12 (1.8%)       | 3 (2.1%)        | 0.3             | 0.737           |
| Lichenoid                       | 91 (14%)        | 23 (16.5%)      | 2.4             | 0.507           |
| Psoriasiform                    | 72 (11.1%)      | 11 (7.9%)       | -3.2            | 0.291           |
| Spongoid                        | 96 (14.8%)      | 9 (6.4%)        | -8.3            | 0.008           |
| Vasculopathic                   | 42 (6.4%)       | 5 (3.5%)        | -2.8            | 0.238           |
| Vesiculobullous                 | 35 (5.4%)       | 10 (7.1%)       | 1.7             | 0.421           |
| **Neoplastic Diseases**         |                 |                 |                 |                 |
| Keratinocytic                   | 68 (10.5%)      | 21 (15.1%)      | 4.5             | 0.139           |
| Melanocytic                     | 21 (3.2%)       | 12 (8.6%)       | 5.3             | 0.007           |
| Other cells                     | 90 (13.9%)      | 14 (10%)        | -3.8            | 0.270           |
| Other                           | 38 (5.8%)       | 9 (6.4%)        | 0.6             | 0.843           |
| Non-diagnostic                  | 82 (12.6%)      | 22 (15.8%)      | 3.1             | 0.334           |
| Total                           | 647(100%)       | 139 (100%)      |                 |                 |

Figure 2. Cases admitted to the dermatology outpatient department in the year preceding (2019) and following (2020) the first nationally announced COVID-19 case.

* P (two-tailed) < 0.05.
and atrophy of the eccrine glands' dermal ducts may result in alopecia and anhidrosis [18].

Pigmented purpuric dermatosis is a capillaritis characterized by petechiae, purpura, and brown-red discoloration [19]. Mycosis fungoides is a T-cell cutaneous lymphoma with various clinical presentations [20]. Clinically, the skin manifestations of these two diseases can sometimes overlap [21]. According to some studies, pigmented purpuric dermatosis is a type of cutaneous lymphoma [22], and persistent cases may be a precursor to mycosis fungoides [23]. Mycosis fungoides should be suspected when there are generalized purpuric lesions that extend beyond the lower extremities and are accompanied by pruritus [24], as opposed to pigmented purpuric dermatosis, which is asymptomatic [25]. Additional studies, such as repeated biopsies, immunopathologic, cytogenetic, and gene rearrangement studies, should be performed in doubtful cases [24].

Histopathological and immunofluorescent studies remain the gold standard in the diagnosis of vasculitic [26] and autoimmune bullous diseases [27]. They are correlated with clinical history, physical examination, and other investigations to distinguish from similar diseases and confirm the diagnosis. There is significant overlap between small vessel vasculitides, making it difficult to distinguish these diseases from skin lesions alone [28]. The presence of gastrointestinal (nausea, vomiting, abdominal pain, melena), renal (nephrotic and nephritic syndrome), joint (arthritis, arthralgia) symptoms, and IgA accumulation in skin or kidney biopsies should raise the possibility of IgA vasculitis [28,29]. Although IgA vasculitis is most common between the ages of 3 and 15, it can occur at any age between 5 months and 89 years old [28,29]. IgA vasculitis in adults is typically limited to the skin [29]. However, all patients should be monitored for long-term systemic involvement [28,30].

To distinguish between autoimmune bullous diseases, histopathological, direct and indirect immunofluorescence methods are used in addition to clinical features [31]. Pemphigus vulgaris is distinguished by flaccid bullae and painful mucosal and skin erosions, as well as a positive Nikolsky sign [32]. Although the Nikolsky sign is also positive in pemphigus foliaceus, mucosal lesions are uncommon. Small flaccid bullae are occasionally encountered, but crusts and erosions are more common [31]. Bullous pemphigoid, on the other hand, is characterized by tense bullae that develop after extremely itchy erythematous urticarial patches and plaques that can last for weeks to months, with mucosal involvement ranging from 10% to 30% [31,32].

Finally, contact dermatitis is a great imitator, presenting with erythematous or purpuric plaques, edematous plaques, vesicles, bullae, crusts, papules, scales, lichenification, and other lesions [33,34]. Despite its origins as a spongiotic disease, it is frequently used as a differential diagnosis in our study for a variety of inflammatory diseases. The most crucial aspect of making a diagnosis is combining the history (particularly occupational) with the distribution of the lesions. Although patch testing is the gold standard in allergic contact dermatitis, potential allergens should be evaluated in terms of clinical significance. The diagnosis of irritant contact dermatitis is usually made by exclusion [35].

In neoplastic diseases, the biopsies were mostly performed to either differentiate between premalignant (acanthotic keratosis, Bowen's disease) and malignant (basal and squamous cell carcinoma, malignant melanoma, mycosis fungoides) lesions or to confirm the diagnosis and guide the treatment. Thus the diagnostic spectrum is straightforward. The relatively low number of dysplastic nevus and malignant melanoma cases could be explained by the fact that this study only used data from the dermatology department, and patients are referred to surgery in doubtful cases to ensure careful control of surgical margins. Excision of small lesions, typically less than 5mm in size, accounts for the high number of benign melanocytic nevi. The various neoplasms caused by other cells are mostly overshadowed by the abundance of benign proliferations (acrochordons and cysts) that are mostly submitted for legal concerns.

The remaining reports diagnosed a wide range of diseases, with the most common goal being to distinguish morphea from extra-genital lichen sclerosus, verruca vulgaris from verrucous or squamous cell carcinoma, and dermatophytosis from erythema annulare centrifugum or psoriasis.

Circumscribed morphea appears as an oval plaque on the trunk with an ivory sclerotic center and erythematous-violaceous borders [36]. It is associated with dyspigmentation (usually hyperpigmentation) and an increase in local temperature [36]. Extragenital involvement is seen in 6%-20% of lichen sclerosus patients [37]. The inner thighs [38] and submammary region [37,38] are frequently affected. Circumscribed plaques or clustered guttate lesions are distinguished by pale atrophic skin and follicular plugging [37]. It is worth remembering that these two diseases share a common pathogenetic basis and can coexist in the same patient [39].

Although the diagnosis of viral warts is usually straightforward, slowly growing large exophytic lesions with a papillomatous or verrucous surface and a tendency to compress deep tissues should be considered for verrucous carcinoma, a subtype of squamous cell carcinoma [40]. These lesions are more common in older men and can be found in the oral mucosa, anogenital region, or plantar region [40,41]. The presence of verruca vulgaris in a high number of pathology reports could also be explained by therapeutically excised samples being submitted for legal reasons.

Dermatophytosis infections can change clinically as a result of drug use, particularly topical corticosteroids, and can be confused with other papulosquamous diseases. Although
The total number of pathology reports was reduced by 77.4% as a result of the shift in clinical decision making to balance patient care and prevent viral transmission. The biopsy rate for clinically benign presentations was reduced, and others were prioritized in order to rule out malignancy. Despite a decrease in the overall number of cases, the rate of pathology reports diagnosing keratinocytic and melanocytic neoplasms increased, while the rate of spongiotic diseases decreased. The frequency of reports involving neoplasms other than keratinocytic and melanocytic cells has also decreased.

Following the pandemic, the total number of patients applying to the dermatology outpatient department decreased by 33.6%, and several differences in case distribution were observed. There was an increase in eczematous diseases, which could be attributed to increased hand washing and disinfectant use. Because patients receiving immunosuppressive treatments required close monitoring during this time period, the number of patients admitted with autoimmune bullous diseases increased. An increase in patients who self-medicate without consulting a doctor may have led to an increase in admissions for urticaria, angioedema, and drug-related eruptions. Moreover, admission rates for infectious skin diseases (primarily bacterial and fungal) during this time period. Admissions for adnexal diseases (primarily acne and rosacea), papulosquamous diseases (psoriasis, pityriasis rubra pilaris, and pityriasis rosea), pigmentary disorders (vitiligo, melasma), and benign neoplasms (nevus, seborrheic keratosis, and various cysts) were significantly reduced.

Several studies examine the post-pandemic period from various perspectives and report similar findings. Admissions to dermatology outpatient departments [47–50], samples submitted to pathology [51] and cytology [52,53] laboratories, and elective surgical procedures performed [54,55] all decreased; however, the distribution of cases varied depending on the region where the study was conducted.

One significant limitation of this study is that the results are dependent on a variety of factors such as the study’s time period and location, the practice habits of the participating physicians, and the available patient population. Another major limitation is the difficulty in classifying diseases both dermatologically and pathologically. To address this limitation, we took a broader approach, excluding variations and subtypes of the same diseases in order to represent cases across a broader spectrum.

The study’s strengths include the fact that it was carried out with a large number of cases over a 4-year period in a dermatopathology referral center, and that when new findings are obtained, they are thoroughly discussed over weekly meetings to ensure strong clinicopathological correlation. The rate of non-diagnostic cases remained stable throughout the COVID-19 year, as clinicopathological correlation of cases was continued through online channels rather than weekly meetings.

A trained eye and open mind is essential in the diagnosis of skin diseases, but additional investigations may be required for some challenging cases. While histopathological techniques are extremely useful, it should be noted that they, too, have limitations and cannot always produce a definitive diagnosis alone. Maintaining clinicopathological correlation and continuous communication between dermatologist and pathologist, in our experience, can increase the likelihood of reaching a diagnosis by up to 75.3%.

References


Adiponectin Contributes to the Inflammatory Milieu in Hidradenitis Suppurativa

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Key words: adiponectin, hidradenitis suppurativa, cytokines, inflammation, immune system

Introduction: Hidradenitis suppurativa (HS) is a severe chronic skin disease. Although the pathogenesis remains unclear, at the basis of HS there is an enhancement of the immune and inflammatory response together with a susceptibility to environmental factors. Cytokine dysregulation is crucial in HS severity and progression.

Objectives: The aim of this study was to analyze serum levels of different cytokines focusing on adiponectin concentration and its oligomers in HS patients compared to both obese and healthy subjects.

Methods: The concentrations of adiponectin and cytokines were measured using enzyme-linked immunosorbent assay (ELISA); the oligomeric distribution of adiponectin (low molecular weight (LMW), medium molecular weight (MMW) and high molecular weight (HMW) oligomers) was evaluated through Western Blotting analysis.
Introduction

Hidradenitis suppurativa (HS) is a complex, chronic inflammatory skin disease characterized primarily by a dysregulation of the innate immune system and by a chronic inflammation that is not only restricted to skin but, especially in severe cases, affects different tissues and organs [2,3]. In particular, the over-activated immune cell infiltration, that is at the basis of HS disease, enhances the inflammatory response through the secretion of a considerable quantity of pro-inflammatory (IL-1β, TNFα, IL-17, INFγ) as well as anti-inflammatory cytokines (IL-10) and chemokines [4-6]. On the other hand, an immunological “priming” in HS comes also from environmental factors such as, smoking-related inflammatory mediators and obesity related pro-inflammatory signals [7]. In particular, in obesity, the increased adipose tissue determines a pro-inflammatory environment due to the imbalance in production of adipokines that contributes to severity and progression of HS disease [8,9]. Recently, it was described a functional interplay among adipose tissue and other organs and tissues whom dysregulation has a key role in inflammation. Indeed, adipose tissue is an endocrine organ that produces several adipocytokines among which adiponectin exerts multivalent beneficial functions; it is abundantly secreted in serum where it circulates as oligomers of different molecular weight: low molecular weight (LMW), medium molecular weight (MMW) and high molecular weight (HMW) [10]. The HMW are the most biologically active oligomers [11]. Adiponectin is involved in the regulation of energy homeostasis, insulin sensitivity and inflammation [12]; interestingly, adiponectin expression is up-regulated in different inflammatory diseases and in some auto-immune diseases, while is down-regulated in metabolic diseases [13]. Regarding hidradenitis, serum adiponectin concentrations were found to be significantly lower, while the levels of the other adipocytokines have been found significantly higher than in controls [14,23].

The aim of this study was to analyze the serum concentrations of 27 cytokines and the most abundant adipocytokine, the adiponectin, in patients affected by HS to investigate the potential relationships with metabolic parameters, disease severity and the risk of HS. We examined cytokines, adiponectin as potential biomarkers of inflammation in HS.

Objectives

To better understand the nature of inflammation in HS and the potential cross link with adipose tissue (AT), the aim of our study was to analyze the expression of different cytokines focusing on adiponectin concentrations and its oligomeric distribution in serum of HS patients respect to both obese and healthy subjects.

Methods

Participants

Fifty-three patients (31 females, 22 males), aged 30.0 ± 13.0 years, were recruited from the Dermatology Unit of the Università degli Studi della Campania “Luigi Vanvitelli”. Subjects were excluded from our study if they met any of the following criteria: age < 18 years, body mass index (BMI) < 17 or > 35, major metabolic disorders (type 2 diabetes, cardiovascular disorders, metabolic syndrome), the presence of concomitant inflammatory cutaneous or systemic disorders and the presence of cancer; were excluded also the patients receiving any systemic treatment which could interfere with the studied parameters. Disease staging was based on the three-degree scale proposed by Hurley. The mean BMI of 29.67 ± 6.1 kg/m² qualified our patients as overweight. The smoker rate amounted to 62.3%. Forty-two healthy volunteers were recruited from the CEINGE staff, they aged 29.67 ± 6.1 kg/m² qualified our patients as overweight. The smoker rate amounted to 62.3%. Forty-two healthy volunteers were recruited from the CEINGE staff, they aged 33 ± 12.0 years old and constituted the control group (BMI = 23.3 ± 3.0); 53 obese subjects, aged 33±12 years old (BMI = 48.4 ± 9.4), were recruited from the Foundation “Salvatore Maugeri” Telesì, Italy [15]. All HS patients fulfilled the established HS diagnostic criteria. All subjects signed an informed consent form. The study was approved.

Results: Total adiponectin is statistically higher in HS patients compared to matched controls and obese subjects. Interestingly, Adiponectin oligomerization state is altered in HS, with an increase of HMW oligomers. Serum levels of PDGF-BB, IL-1β, IL-5, IL-6, IL-12, IL-13, IL-15, IL-17, GMCSF, INFγ, VEGF and MCP-1 are statistically higher while IL-1ra and RANTES levels are statistically lower in HS patients compared to healthy controls. Interestingly, adiponectin positively correlates with PDGF-BB, and IL-13.

Conclusions: Our data confirmed that the complex network that links metabolism to immune homeostasis is dysregulated in HS and that adiponectin and its HMW oligomers are actively involved in this disease. In addition, the correlation between adiponectin and PDGF-BB, and IL-13 extends the role of this adipokine in modulation of the immune response, in particular regulating the innate immune system rather that the adaptive one. Further researches are needed to clarify the complex inflammatory milieu that characterizes HS syndrome.
by the Ethic Committee of the Università degli Studi della Campania “Luigi Vanvitelli” (Prot. 12478/20).

**Anthropometric and Biochemical Measurements**

Blood samples from 53 HS patients, 42 healthy subjects and 53 obese subjects were collected after a 12-hours overnight fasting period and centrifuged to collect serum. Serum aliquots were immediately frozen in liquid nitrogen and stored at -80°C. For all participants total cholesterol, triglycerides, glycemia, C-Reactive Protein were measured (Table 1). The concentration of total adiponectin was measured in triplicate by an enzyme-linked immunosorbent assay (ELISA) as previously described [16].

The levels of 27 cytokine species (PDGF-BB, IL1β, IL1ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, Eotaxin, FGF, GCSE, GMCSF, INFγ, IFNγ, IP10, MCP-1, IP1α/IP1β, RANTES, TNFa, VEGF) were measured in 30 HS patients and in 39 healthy controls using a commercially available kit (Bio-Plex Pro™ Human Cytokine 8-plex Assay). The assay was performed according to the manufacturer’s instructions and the concentrations of cytokines were calculated by comparing reads with a 5-parameter logistic standard curve using a Bioplex-200 instrument (Bio-Rad).

**Western Blotting Analysis of Serum Adiponectin**

Five micrograms of total serum proteins were treated and subjects to electrophoresis as previously described [17]. The blots were developed by ECL (Amersham Biosciences) with the use of Kodak BioMax Light film and digitalized with a scanner (1.200 dpi) and analyzed by densitometry with the ImageJ software. Each serum sample was tested 2 times in duplicate.

**Statistical Analysis**

Data is expressed as average ± standard deviation (SD) and median. The meanings of the differences in biochemical parameters between the groups were determined using the Mann-Whitney test and the Chi-square test. To evaluate the relationship with median adiponectin levels, multiple logistic regression was performed. A P value <0.05 was considered to indicate statistically significant results.

**Results**

**Baseline Features and Serum Levels of Adiponectin in HS Patients**

The anthropometric and biochemical characteristics of HS patients, sex and age-matched obese and healthy subjects are shown in Table 1. We found statistically significant difference in BMI between HS patients and controls (29.67 ± 6.12 versus 23.3 ± 3.04, P < 0.00) as well as for total adiponectin serum levels (28.25 μg/ml ± 4.49 versus 24.67 μg/ml ± 3.35, P < 0.01); both parameters result significantly higher in HS patients compared to controls. The statistical analysis indicated that the increase of adiponectin levels in HS is independent from BMI and sex, 2 potential confounding factors. Statistical analysis did not reveal significant difference in adiponectin concentrations among the HS groups based on the three Hurley degrees of disease severity. HS Hurley degree of HS patients are reported in Table 1: 30.2% of the patients have a Hurley I, 52.8% Hurley II and 17.0% Hurley III degree of disease severity.

As in literature was reported an opposite trend and to further validate the findings on concentration of adiponectin, we measured the levels of this adipokine in a cohort of 53 obese patients; as shown in Table 1, the comparison of

<p>| Table 1. Clinical, biochemical and anthropometrical characteristics of HS, obese patients and healthy subjects. |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>HS patients (N 53)</th>
<th>Obese subjects (N, 53)</th>
<th>Controls (N 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F), N (%)</td>
<td>31 (53.8)</td>
<td>33 (62.3)</td>
<td>20 (47.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age mean (±SD), years</td>
<td>30±13</td>
<td>33±12</td>
<td>33±12</td>
<td>0.37</td>
</tr>
<tr>
<td>BMI mean (±SD)</td>
<td>29.67 ± 6.12</td>
<td>48.4 ± 9.4</td>
<td>23.3 ± 3.04</td>
<td>0.00</td>
</tr>
<tr>
<td>Cholesterol mean (±SD) (mg/dL)</td>
<td>203.54 ± 44.16</td>
<td>169.94 ± 37.21</td>
<td>191.48 ± 35.22</td>
<td>0.00</td>
</tr>
<tr>
<td>Triglycerides mean (±SD) (mg/dL)</td>
<td>103.62 ± 36.97</td>
<td>146.81 ± 102.54</td>
<td>82.86 ± 50.31</td>
<td>0.00</td>
</tr>
<tr>
<td>Glycemia mean (±SD) (mg/dL)</td>
<td>94 ± 19</td>
<td>87 ± 28</td>
<td>86 ± 17</td>
<td>0.17</td>
</tr>
<tr>
<td>C-Reactive Protein mean (±SD) (mg/L)</td>
<td>6.87 ± 8.36</td>
<td>8.23 ± 8.48</td>
<td>-</td>
<td>0.41</td>
</tr>
<tr>
<td>Hurley I (%)</td>
<td>16 (30.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hurley II (%)</td>
<td>28 (52.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hurley III (%)</td>
<td>9 (17.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adiponectin mean (±SD) (μg/mL)</td>
<td>28.54 ± 4.49</td>
<td>20.06 ± 4.71</td>
<td>24.67 ± 3.35</td>
<td>0.00</td>
</tr>
</tbody>
</table>

BMI = body mass index; HS = hidradenitis suppurativa; SD = standard deviation.
Cytokine Concentration in HS Patients and Healthy Controls

To better explore the inflammatory milieu in serum from HS patients, we analyzed a panel of 27 different cytokines (PDGF-BB, IL1β, IL1ra, IL2, IL4, IL5, IL6, IL7, IL8, IL9, IL10, IL12, IL13, IL15, IL17, Eotaxin, FGF, GCSF, GMCSF, INFγ, IP10, MCP-1, IP1α, IP1β, RANTES, TNFα, VEGF). We tested 30 HS patients and 39 controls. The results demonstrated that, among the others, PDGF-BB, IL-1β, IL-5, IL-6, IL12, IL13, IL15, IL17, GMCSF, INFγ, VEGF and MCP-1 levels were statistically higher while IL-1ra and RANTES levels were statistically lower in the serum of HS patients compared to healthy controls (Table 2).

Next, to investigate whether adiponectin is functionally related with any tested cytokines, we divided the HS patients in two subgroups using the median value of adiponectin concentration (27.8 μg/mL) as an arbitrary cut-off. According to adiponectin concentrations, patients with higher adiponectin concentrations (ie with values above the median) represented subgroup 1 and patients with lower adiponectin concentrations (ie with values under the median) represented subgroup 2. Statistical analysis performed using the univariate model showed that the patients with higher levels of adiponectin (subgroup 1) have also significantly higher PDGF-BB and a similar trend versus IL-13 (Table 3).

**Conclusions**

Hidradenitis (HS) is a severe chronic inflammatory skin disease primarily due to the alteration of immunity and to chronic inflammation [2,18]. A functional interconnection between immune system and adipose tissue, link observed in patients affected by metabolic disorders in which the dysregulation of energy metabolism negatively affects the immune biochemical parameters between HS patients and obese subjects showed a statistically differences in BMI (29.67 ± 6.12 versus 48.4 ± 9.4, P < 0.00) as well as in adiponectin levels; these latter are higher in HS than in obese patients (28.25 μg/ml ± 4.49 versus 20.06 μg/ml ± 4.71, P < 0.00).

**Oligomeric Distribution of Adiponectin in HS Patients**

To better investigate the involvement of adiponectin in HS patients, we examined the oligomeric profile of this adipokine through the visualization of HMW, MMW and LMW oligomers. Western blot evidenced that the HMW and MMW adiponectin oligomers are increased in serum of HS patients if compared to obese and healthy subjects (Figure 1, P < 0.05).

![Figure 1](image_url). Western blotting analysis shows that adiponectin HMW and MMW oligomers are statistically higher in serum from HS patients compared to obese and healthy subjects. (A) Representative WB image of adiponectin different oligomers (HMW, MMW, LMW) from four HS patients, four obese subjects and four controls. (B) Graphical representation of pixel quantization of adiponectin oligomers analysed in 53 HS patients, 53 obese subjects and 42 controls. For other details see materials and methods. P < 0.05.
component of the body protective systemic response to the chronic inflammatory processes and immune system alterations [17,18,21].

In this study, to investigate the nature of the inflammatory milieu in HS and the potential contribute of adipose tissue, we analyzed several cytokines focusing on the most abundant adipokine, ie adiponectin and its oligomeric profile. Interestingly, system and viceversa. Indeed, in obese or overweight people there is a greater frequency of autoimmune diseases such as rheumatoid arthritis, type I diabetes and HS [24]. This functional interconnection is guaranteed by the hormonal activity of the adipose tissue through the secretion of adipokines such as adiponectin. In literature, numerous studies support the hypothesis that high levels of adiponectin represent a key component of the body protective systemic response to the chronic inflammatory processes and immune system alterations [17,18,21].

In this study, to investigate the nature of the inflammatory milieu in HS and the potential contribute of adipose tissue, we analyzed several cytokines focusing on the most abundant adipokine, ie adiponectin and its oligomeric profile. Interestingly,

Table 2. Cytokine levels (pg/ml) in HS patients and healthy subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls (N 39)</th>
<th>HS patients (N 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>22 (56%)</td>
<td>11 (37%)</td>
<td>0.096</td>
</tr>
<tr>
<td>F</td>
<td>17 (44%)</td>
<td>19 (63%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age, mean (±SD)</td>
<td>33.8 (6.8)</td>
<td>29.6 (13.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>BMI, mean (±SD)</td>
<td>25.5 (3.7)</td>
<td>26.6 (3.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>IL-1β, mean (±SD)</td>
<td>2.0 (0.5)</td>
<td>2.3 (0.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>IL-12, mean (±SD)</td>
<td>11.3 (1.3)</td>
<td>13.5 (3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-13, mean (±SD)</td>
<td>5.5 (1.1)</td>
<td>8.4 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-15, mean (±SD)</td>
<td>347.2 (25.0)</td>
<td>390.3 (38.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-17, mean (±SD)</td>
<td>25.0 (3.9)</td>
<td>27.2 (5.2)</td>
<td>0.048</td>
</tr>
<tr>
<td>GM-CSF, mean (±SD)</td>
<td>12.8 (0.7)</td>
<td>14.5 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCP-1 (MCAF), mean (±SD)</td>
<td>36.9 (15.0)</td>
<td>56.1 (31.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>RANTES, median (IQR)</td>
<td>6833.4 (5469.2, 8214.1)</td>
<td>45145.1 (20829.6, 93670.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDGF-BB, median (IQR)</td>
<td>1638.5 (1180.5, 1991.2)</td>
<td>2306.6 (1701.6, 3208.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-1ra, median (IQR)</td>
<td>371.5 (333.0, 446.4)</td>
<td>333.0 (257.0, 400.0)</td>
<td>0.036</td>
</tr>
<tr>
<td>IL-5, median (IQR)</td>
<td>52.3 (49.0, 55.5)</td>
<td>58.5 (52.3, 67.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>IL-6, median (IQR)</td>
<td>7.6 (7.0, 8.1)</td>
<td>9.0 (7.8, 10.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VEGF, mean (SD)</td>
<td>417.6 (40.2)</td>
<td>452.3 (52.7)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

BMI = body mass index; HS = hidradenitis suppurativa; SD = standard deviation. Acronym list: IL (interleukin); Granulocyte-Macrophage Colony-Stimulating (GM-CSF); Interferon (INF); Monocytes Chemoattractant Protein(MCP); Platelet-Derived Growth Factor-BB (PDGF-BB); Vascular Endothelial Growth Factor (VEGF).

Table 3. Univariate analysis of anthropometric, clinical parameters and cytokines levels (pg/ml) on the basis of adiponectin levels: median value of adiponectin (27.8 μg/ml) was used as an arbitrary cut-off.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adiponectin ≤ 27.8</th>
<th>Adiponectin &gt; 27.8</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N = 14</td>
<td>N = 16</td>
<td></td>
</tr>
<tr>
<td>Sex M, N (%)</td>
<td>7 (50%)</td>
<td>4 (25%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex F, N (%)</td>
<td>7 (50%)</td>
<td>12 (75%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Age, mean (±SD)</td>
<td>30.1 (12.1)</td>
<td>29.3 (15.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>BMI, mean (±SD)</td>
<td>27.3 (3.7)</td>
<td>26.0 (4.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>PDGF-BB, median (IQR)</td>
<td>2984.9 (2226.8, 3463.2)</td>
<td>1823.9 (1306.3, 2507.5)</td>
<td>0.020</td>
</tr>
<tr>
<td>IL-5, median (IQR)</td>
<td>61.5 (55.5, 65.7)</td>
<td>55.5 (48.1, 68.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>IL-13, median (IQR)</td>
<td>8.8 (7.3, 9.7)</td>
<td>5.8 (4.9, 9.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>GM-CSF, median (IQR)</td>
<td>14.7 (13.9, 15.5)</td>
<td>13.5 (12.7, 15.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hurley I</td>
<td>5 (36%)</td>
<td>6 (38%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hurley II</td>
<td>5 (36%)</td>
<td>6 (38%)</td>
<td></td>
</tr>
<tr>
<td>Hurley III</td>
<td>4 (29%)</td>
<td>4 (25%)</td>
<td></td>
</tr>
</tbody>
</table>
we found increased levels of adiponectin and HMW oligomers in HS patients compared to both healthy and obese subjects independently from BMI. To our knowledge, there are two studies describing adiponectin concentration in HS that found decreased serum level of adiponectin in the patients [22,23]. The discrepancy with our results may be traced back to clinical and biochemical differences of the considered patients: the study by Malara et al. analyzed patients with a very high BMI (33 versus 29.6 of our cohort), while González-Lopez considered a cohort of patients with a more severe clinical phenotype of HS [22,23]. It is to notice, however, that we excluded that BMI might represent a confounding factor for adiponectin expression in HS patients; indeed, HS patients are more likely to have obesity and metabolic syndrome and overweight people have a greater incidence of HS [24].

In addition, although the significance of the molecular distribution of adiponectin is still largely unknown, it has been shown that the HMW oligomers have a stronger biological meaning and is the most important contributor to adiponectin functions [10]. Our findings that HS is associated with high circulating adiponectin levels, combined with a shift towards the HMW forms reinforce the hypothesis that adiponectin has a strong functional role in regulating inflammation in HS. The specificity of adiponectin role in HS is confirmed also by the significant difference of its concentrations that we found in the two populations, HS and obese subjects.

Next, in this study, we analyzed different cytokine expression previously reported to spill-over from the skin lesions into the systemic circulation resulting in heightening risk for systemic inflammation in HS patients [1]. Among the others, we found that PDGF-BB, IL-1β, IL-5, IL-6, IL-12, IL-13, IL-15, IL-17, GMCSF, INFγ, VEGF and MCP-1 levels are statistically higher in HS patients while IL-1ra and RANTES levels are statistically lower in the serum of HS patients compared to healthy controls. Serum cytokine levels are very often altered in HS patients [25,23]. In accordance with our data, the levels of the pro-inflammatory IL-17 cytokine, whose production is made by neutrophils and Th17 cells, is increased in HS patients [26,27]. IL-17 is crucial in determining the inflammatory process of HS, inducing the expression of other pro-inflammatory cytokines, such as IL1β and TNFα and stimulating the activation of adaptive immune cells [1,28]. On the other hand, one study found no differences in IL-17 levels between patients and controls [29]. Regarding IFN-γ, no statistically decrease was found in the serum of HS patients while a significant difference was found in another study [7].

Although not significant, our data also evidenced that IL-10 is higher in HS patients than in controls suggesting that the immune system is compensating the dysregulation in Th1/Threg ratio typical of HS compatible with the mild phenotype of most of our patients. In accordance with our results, increased serum IL-10 levels compared to control was reported in one study [30]; in two other studies no statistical difference was found [31,32].

Finally, for the first time, we correlated cytokines expression level to adiponectin concentration. We found that adiponectin correlates with PDGF-BB, and IL-13 but not with IL-17, IL-1β, and INFγ suggesting that adiponectin function might be related to the innate immune system activation rather than the adaptive one, exerting anti-inflammatory actions. Previously, adiponectin has been demonstrated to directly and specifically bind PDGF-BB in smooth muscle cells suppressing their proliferation and migration [33] suppressing the development of atherosclerosis, promoting inflammation. Arita et al. demonstrated that the inhibitory effects of adiponectin towards PDGF-BB result in suppression of vasculogenesis and inflammation [33]. The association between adiponectin and PDGF-BB in HS patients suggests that the adipokine probably counteracts the inflammatory process triggered by the disease.

As IL-13 has been described as anti-inflammatory factor in the adipose tissue, the direct correlation with adiponectin further confirms that adiponectin is acting as anti-inflammatory molecule [34]. In addition, IL-13 has been involved in the maintenance of macrophages in an anti-inflammatory state as M2 phenotype supporting the hypothesis that adiponectin might participate in the regulation of the innate immune response [35].

There are two main limitations in the present study, one is the relatively small number of patients and the other is the absence of a large cohort of severe patients. In addition, the great heterogeneity in age, gender, environmental factors and potential comorbidities among the HS analyzed patients in different studies may be at the basis of the variability found in the expression of cytokines.

In conclusion, our data confirmed that the complex network that links together metabolism to immune homeostasis is dysregulated in HS and that adiponectin and its HMW oligomers are not only actively involved in the HS but that interacts with the complex inflammatory systemic milieu made by pro-inflammatory cytokines. In addition, the correlation between adiponectin and PDGF-BB, and IL-13 extends the role of this adipokine in modulation of the immune response suggesting that adiponectin might act regulating the innate immune system rather than the adaptive one. Further researches are needed to clarify the complex inflammatory milieu that characterizes HS syndrome.

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Dermoscopy of the Diverse Spectrum of Cutaneous Tuberculosis in the Skin of Color

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Key words: dermoscopy, cutaneous tuberculosis, lupus vulgaris, scrofuloderma

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Introduction: Cutaneous tuberculosis is an uncommon form of tuberculosis, accounting for 1%-2% of all forms of extra-pulmonary tuberculosis. Knowledge of the dermoscopic characteristics of different clinical types of cutaneous tuberculosis can help timely diagnosis resulting in better outcomes.

Objectives: To characterize the Dermoscopy findings in different clinical types of cutaneous tuberculosis in the skin of color.

Methods: All clinically suspected and biopsy confirmed cases of cutaneous tuberculosis seen from July 2019 through December 2021 were retrospectively recruited. Information including age, gender, disease duration, site and morphology of lesions, and presence of concomitant tuberculosis elsewhere was noted. Two investigators retrospectively reviewed the dermoscopic characteristics of these cases.

Results: Twenty-two patients comprised of 12 women and 10 men met the inclusion criteria. Lupus vulgaris was the commonest presentation of cutaneous tuberculosis seen in 13 patients. Five had scrofuloderma, 2 had tuberculosis verruca cutis and 1 patient each had lichen scrofulosorum and papulo-necrotic tuberculid. Yellow-orange structureless areas (100%), linear/dot vessels (100%), white scales (92.3%), and white structureless areas (84.6%) were the predominant dermoscopy findings in lupus vulgaris. In scrofuloderma, linear vessels and white structureless areas were visible in all cases. Dirty white scales with a papillated surface were characteristically seen in tuberculosis verruca cutis, with 1 of the 2 patients each showing vessels and yellow-orange structureless areas. White globules with surrounding erythema were seen in lichen scrofulosorum and yellow-orange structureless areas with keratin plugs in papulo-necrotic tuberculid.

Conclusions: A thorough understanding of the characteristic dermoscopy of cutaneous tuberculosis can help suspect the diagnosis early resulting in better management opportunity.
Introduction

Dermoscopy is widely used for diagnosing various inflammatory, neoplastic and pigmentary dermatoses. Its utility in suspecting infective as well as granulomatous diseases is progressively established. Cutaneous tuberculosis is an uncommon form of tuberculosis, accounting for 1%-2% of all forms of extra-pulmonary tuberculosis, however the associated morbidity warrants prompt diagnosis and treatment [1]. In India, lupus vulgaris (LV) is the most frequent clinical type reported in adults and scrofuloderma in children [2]. Knowledge of the dermoscopy characteristics of different clinical types of cutaneous tuberculosis can help timely diagnosis resulting in better treatment outcomes.

Objectives

To characterize the Dermoscopy findings in different clinical types of cutaneous tuberculosis in dark skin phototypes. The available literature on the dermoscopy of diverse spectrum of cutaneous tuberculosis is limited; thus, the present study was planned to bridge this knowledge gap.

Methods

All clinically suspected and biopsy confirmed cases of cutaneous tuberculosis seen from July 2019 through December 2021 (2 and a half years) were retrospectively recruited. Detailed information regarding age, gender, disease duration, site and morphology of lesions, and presence of concomitant tuberculosis elsewhere was noted. The final analysis was done only for cases where a skin biopsy was performed and dermoscopy images were available. Dermoscopy was performed in these cases as a routine, and images were captured with iPhone 11 (12-megapixel camera; Apple Inc., Cupertino, California) attached to Dermlite DL200 hybrid (10x magnification, 3Gen, San Juan Capistrano, California). Two investigators (RJ, PC) retrospectively reviewed the dermoscopic characteristics of these cases. The dermoscopy findings were recorded following the standardized terminology according to the International Dermoscopy Society (IDS) consensus document on dermoscopy in general dermatology (3). Statistical analysis was performed using SPSS software (version 22; SPSS Inc.). Categorical variables were expressed as number and percentage, and numerical data were expressed as mean and standard deviation. Being a retrospective study institutional review board approval was not required.

Results

Twenty-two patients with cutaneous tuberculosis, 12 women and 10 men, met the inclusion criteria. LV was the commonest presentation of cutaneous tuberculosis seen in 13 patients. Five had scrofuloderma, 2 had tuberculosis verrucosa cutis (TVC) and 1 patient each had lichen scrofulosorum and papulo-necrotic tuberculid (PNT). The face was the most frequent site involved; 7 patients of LV and 4 of scrofuloderma had facial lesions (Table 1). A primary focus was identified in the patient with PNT; however, no focus could be recognized in the girl with lichen scrofulosorum despite an extensive search. None of the patients with LV, scrofuloderma, and TVC had concomitant tuberculosis elsewhere. Dermoscopy images were evaluated for the diverse morphology of cutaneous tuberculosis (Table 2).

Table 1. Clinical and demographic characteristics of patients with cutaneous tuberculosis.

<table>
<thead>
<tr>
<th>Type of Cutaneous TB</th>
<th>Number of cases</th>
<th>Male: Female, N</th>
<th>Fitzpatrick skin type, N</th>
<th>Age Mean ± SD (years)</th>
<th>Duration Mean (range), months</th>
<th>Site, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus vulgaris</td>
<td>13</td>
<td>4:9</td>
<td>III: 3 IV: 5 V: 5</td>
<td>33.7±18.9</td>
<td>11 (2-30)</td>
<td>Face (7) Neck (1) Upper limb (3) Lower limb (2)</td>
</tr>
<tr>
<td>Scrofuloderma</td>
<td>5</td>
<td>3:2</td>
<td>III: 1 IV: 2 V: 2</td>
<td>33.2±19.8</td>
<td>9.6 (6-12)</td>
<td>Face (4) Neck (1)</td>
</tr>
<tr>
<td>Tuberculosis verrucosa cutis</td>
<td>2</td>
<td>2:0</td>
<td>IV:1 V:1</td>
<td>17 and 42 years</td>
<td>24 and 36 years</td>
<td>Upper limb (2)</td>
</tr>
<tr>
<td>Lichen scrofulosorum</td>
<td>1</td>
<td>Female</td>
<td>IV</td>
<td>12 years</td>
<td>9</td>
<td>Trunk &amp; Extremities</td>
</tr>
<tr>
<td>Papulonecrotic tuberculid</td>
<td>1</td>
<td>Male</td>
<td>IV</td>
<td>32 years</td>
<td>4</td>
<td>Legs and feet</td>
</tr>
</tbody>
</table>

SD = standard deviation; TB = tuberculosis.
### Table 2. Dermoscopic characteristics of diverse morphology of cutaneous tuberculosis.

<table>
<thead>
<tr>
<th>Dermoscopic characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus vulgaris (N = 13)</td>
<td></td>
</tr>
<tr>
<td>• Yellow orange structureless areas</td>
<td>13 (100)</td>
</tr>
<tr>
<td>• Linear vessels with or without branches</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>• Dot vessels</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>• Black dot/ globules</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>• White lines</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>• White structureless areas</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>• Follicular plugging</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>• White scales</td>
<td>12 (92.3)</td>
</tr>
<tr>
<td>• Bluish hue</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>• Ulceration</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>• Perilesional white halo</td>
<td>7 (53.8)</td>
</tr>
<tr>
<td>Scrofuloderma (N = 5)</td>
<td></td>
</tr>
<tr>
<td>• Yellow orange structureless areas</td>
<td>4 (80)</td>
</tr>
<tr>
<td>• Linear vessels with or without branches</td>
<td>5 (100)</td>
</tr>
<tr>
<td>• Sero-sanguineous crust</td>
<td>3 (60)</td>
</tr>
<tr>
<td>• White structureless areas</td>
<td>5 (100)</td>
</tr>
<tr>
<td>• Orange-brown scale</td>
<td>3 (60)</td>
</tr>
<tr>
<td>• Ulceration</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Tuberculosis verrucosa cutis (N = 2)</td>
<td></td>
</tr>
<tr>
<td>• Dirty white scale with papillated surface</td>
<td>2 (100)</td>
</tr>
<tr>
<td>• Dot and linear curved vessels</td>
<td>1 (50)</td>
</tr>
<tr>
<td>• Yellow orange structureless area</td>
<td>1 (50)</td>
</tr>
<tr>
<td>• Hemorrhagic crust</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Lichen scrofulosorum (N = 1)</td>
<td></td>
</tr>
<tr>
<td>• White globules with surrounding erythema</td>
<td>Single patient</td>
</tr>
<tr>
<td>• Peripheral pigment network</td>
<td></td>
</tr>
<tr>
<td>• Focal white scale</td>
<td></td>
</tr>
<tr>
<td>Papulonecrotic tuberculid (N = 1)</td>
<td></td>
</tr>
<tr>
<td>• Yellow-orange structureless area</td>
<td>Single patient</td>
</tr>
<tr>
<td>• Keratin plug</td>
<td></td>
</tr>
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</table>

### Lupus Vulgaris (N = 13)

Eight patients had plaque type of LV and the remaining nodular type. Women (9) outnumber men (4), and the mean age at presentation was 33.7 years. The mean duration of illness was 11 months (range 2-30 months). Yellow-orange structureless areas were consistently visualized in all cases of LV; these represent the epitheloid granulomas seen on histopathology (Figure 1, A-D). Linear vessels with and without branches were appreciated in 11 (84.6%) patients and dot vessels in 3 (23.1%) patients. The focal white scale was another frequent feature seen in 12 (92.3%) lesions. White lines (unspecified) and white structureless areas were seen in 10 (76.9%) and 11 (84.6%) cases, respectively (Figure 1, A, B and D). Follicular plugging was visible dermoscopically in 8 (61.5%), and a peri-lesional halo of hypopigmentation was observed in 7 (73.8%) patients (Figure 1, A and D).

### Scrofuloderma (N = 5)

All patients presented with multiple discharging sinuses and scarring. The mean age of patients was 33.2 years, with a mean duration of lesions being 9.6 months (range 6-12 months). The most consistent dermoscopy findings were linear vessels with and without branches (100%), white structureless areas (100%), and yellow-orange structureless areas (80%) (Figure 2, A and B). Sero-sanguineous crust representing the sinuses and orange-brown scales were appreciated in 60% of patients each (Figure 2, A and B).

### Tuberculosis Verrucosa Cutis (N = 2)

Tuberculosis verrucosa cutis was the morphology of cutaneous tuberculosis in two men aged 17 and 42 years. One of them had the lesion for 2 years and the other for 3 years. Both dermoscopically showed dirty white thick scales with a papillated surface (Figure 2, C and D). However, only 1 had the presence of dot vessels and curved vessels. Yellow-orange structureless areas were visible in one of the patients.

### Lichen Scrofulosorum (N = 1)

The 12-year-old-girl with lichen scrofulosorum presented with multiple grouped skin-colored papules over the trunk and extremities. On dermoscopy, numerous uniform follicular and non-follicular white globules with surrounding erythema and peripheral pigment network were seen (Figure 3A). Some of the white globules had a central black dot. White scales were appreciated focally.

### Papulo-necrotic Tuberculid (N = 1)

The patient was a 32-year-old man with a primary focus of tuberculosis in the brain as a tubercular abscess. He presented with multiple purpuric macules and hyperkeratotic papules and plaques over soles. Dermoscopy showed orange-brown structureless areas and keratin plugs (Figure 3. B and C).

### Conclusions

The application of dermoscopy for granulomatous diseases is gaining recognition as it gives a swift clue to the diagnosis much before histopathology results are accessible. The most available literature is on dermoscopy of LV, including a significant case series from India of 19 cases [4]. For other clinical types, there are anecdotal reports or small case series. Here we report our experience with dermoscopy of distinctive morphological types of cutaneous tuberculosis seen over a 2 and a half year period. A total of 22 patients with a confirmed diagnosis of tuberculosis were seen over the study
period. LV was the most typical clinical type encountered, followed by scrofuloderma.

The hallmark of granulomatous disorders is yellow-orange structureless areas representing the dermal granulomas seen histologically (Table 3) [5-7]. All the patients with LV, the majority (80%) with scrofuloderma, and the single patient with PNT in the presented series showed yellow-orange structureless areas. Ankad et al, in their series of 19 cases with LV, reported the presence of yellow-white globules instead of the yellow-orange structureless areas explained due to a predominance of Fitzpatrick skin type IV/V in their patients [4]. Although most cases in the current series also had Fitzpatrick skin type IV/V, the yellow-orange hue was appreciable. A retrospective study by International Dermoscopy Society reports presence of an orange-yellow hue representing the dermal granulomas in patients with Fitzpatrick skin type V/VI. In their 12 reported patients with LV, focal bright areas were seen in a majority [8]. Similar yellow-orange structureless areas are reported in TVC; however, it was evident only in 1 of our patients [9]. The presence of thick white adherent scales and marked papillomatosis obscured their visibility in the other. Lichen scrofulosorum did not reveal yellow-orange structureless areas, possibly since the granulomas are more petite and centered on the hair follicles.

Figure 1. (A-D) Dermoscopy of lupus vulgaris showing yellow-orange structureless areas (black star), linear vessels with and without branches (black arrow), white structureless areas (blue star) and lines (blue arrowheads), follicular plugging (black circle), white scales (blue arrow), dot vessels (black square) and peri-lesional halo (blue rectangle). (A, inset) A well-defined plaque with atrophy and an advancing erythematous margin.
Figure 2. Dermoscopy of scrofuloderma showing sero-sanguineous crust representing the sinus with yellow-orange structureless areas (black star), white structureless areas (blue star) and linear vessels (black arrow) (A,B), clinical image showing a central sinus surrounded by erythema and scarring (A, inset). Dermoscopy of tuberculosis verrucosa cutis showing thick dirty white scales (blue arrow), yellow orange structureless areas (black star), white structureless areas (blue star) and dot/ curved vessels (blue square) (C,D), clinical image showing hyperkeratotic plaque over middle finger (C, inset).

Linear vessels with or without branches were frequently observed in LV and represent dilated capillary loops that appear well focused because of their displacement towards the epidermis by the underlying granulomas. Vessels were appreciated in all cases with scrofuloderma and TVC; however, PNT and lichen scrofulosorum lacked them. In lichen scrofulosorum, a few white globules showed peripheral erythema representing focal dilatation of the capillaries.

White structureless areas indicating the dermal fibrosis and acanthosis are well reported in LV and were seen in most LV lesions in the written series. 76.9% of patients also had linear white streaks arranged haphazardly and correlated histopathologically with proliferating collagen bundles distributed throughout the dermis. All cases of scrofuloderma also had white structureless areas corroborating the associated scarring evident clinically.

Follicular plugging in LV was reported to be higher in the present series than in literature and was also appreciated in PNT [4]. The serosanguineous crust was noticed in most patients with scrofuloderma and represented sinuses seen clinically; at places, there was an overlying hemorrhagic crust. Dirty white thick scales covered the lesions of TVC, making visualization of underlying structures difficult. The short curved and dot vessels were only visible in one case...
focally. Inconspicuous vessels have been reported by Jakhar et al in TVC, with the prominent finding in their case being a yellow-red background, papillated surface, and dirty thick scales [9]. Pale monomorphic grouped white globules with peripheral erythema and hyperpigmentation seen in our patient with lichen scrofulosorum have been reported in the past [10,11]. However, we could not appreciate telangiectasias as reported in the literature.

Dermoscopy of various morphologies of cutaneous tuberculosis appears noteworthy. For LV, yellow-orange structureless areas, well-focused linear vessels, and white structureless areas and lines appear significant. In scrofuloderma additionally, serosanguineous crust representing the sinuses is noteworthy. Thick white scales and papillomatosis obscure sub-surface changes in TVC. Occasionally focal curved/dot vessels can be appreciated. Grouped monomorphic white globules with a central black dot and surrounding erythema and hyperpigmentation symbolize lichen scrofulosorum. Yellow-orange structureless areas and keratin plugs are appreciable in PNT. A thorough understanding of the characteristic dermoscopy of cutaneous tuberculosis seems necessary, especially for dermatologists working in the

Table 3. Histopathological correlation for dermoscopy characteristics.

<table>
<thead>
<tr>
<th>Dermoscopy characteristic</th>
<th>Histopathological correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow-orange structureless areas</td>
<td>Dermal granulomas</td>
</tr>
<tr>
<td>Linear vessels</td>
<td>Dilated dermal capillaries pushed up by granuloma</td>
</tr>
<tr>
<td>White structureless areas</td>
<td>Dermal fibrosis and acanthosis</td>
</tr>
<tr>
<td>White lines</td>
<td>Dermal collagen bundles with a parallel orientation</td>
</tr>
<tr>
<td>Follicular plugs</td>
<td>Keratin in follicular infundibulum</td>
</tr>
<tr>
<td>Scales</td>
<td>Hyperkeratosis</td>
</tr>
</tbody>
</table>
endemic region. The written case series attempts to bridge the existing gaps in the knowledge about dermoscopy of various clinical morphologies of cutaneous tuberculosis.

References


Alterations of the Human Gut Microbiome in Patients With Hidradenitis Suppurativa: A Case-control Study and Review of the Literature

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**Key words:** hidradenitis suppurativa, inflammatory skin disorders, gut microbiome, pathogenesis

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**ABSTRACT**

**Introduction:** Hidradenitis suppurativa (HS) is a chronic and systemic inflammatory disease that extends beyond the skin. The role of gut microbiome (GM) alterations in the pathogenesis of inflammatory and autoimmune disorders is remarkable.

**Objectives:** Based on the hypothesis that dysbiosis in the GM may trigger systemic inflammation in the pathogenesis of HS, this study aimed to investigate whether the GM is altered in HS patients compared with healthy subjects.

**Methods:** In the present case-control study, fecal samples from 15 patients with HS and 15 age- and sex-matched healthy individuals were collected and analyzed using 16S rRNA-based metagenomic analysis, New Generation Sequencing (NGS). The V3 and V4-hypervariable regions of the bacterial 16S rDNA gene were amplified from all samples and sequenced by the Illumina MiSeq platform. Bioinformatics analyses were performed in QIIME2.

**Results:** Shannon alpha diversity index showed significantly reduced diversity in HS patients (P = 0.048). Bray-Curtis Dissimilarity and Jaccard Distance revealed that the gut microbial composition of HS patients was significantly distinctive from that of controls (P = 0.01 and P = 0.007, respectively). The relative abundance of unclassified Clostridiales, unclassified Firmicutes, and Fusicatenibacter in HS was significantly lower than that in controls (P = 0.005, P = 0.029, and P = 0.046, respectively).

**Conclusions:** This study indicated that significant alterations in the GM of HS patients could play a critical role in the pathogenesis of HS and might be a trigger for systemic inflammation. Increased understanding of the pathogenesis of HS will shed light on the new potential therapeutic targets and novel treatment options.
Introduction

Hidradenitis suppurativa (HS) significantly impacts patients quality of life with its chronic and relapsing course and sub-optimal response to therapy [1]. The etiopathogenesis of the disease has not been elucidated yet. However, it is clear that HS is not simply an inflammatory skin disorder, but a systemic inflammatory disorder [2]. Its associations with inflammatory and autoimmune disorders, increased levels of inflammatory cytokines in sera of patients, and γ-secretase complex mutations leading to impaired notch signaling pathway may suggest a systemic inflammation that distant skin sites might trigger [3].

Recently, a term called “gut-skin axis” has been introduced and highlighted a potential link between the gut microbiome and the skin through complex immune mechanisms [4]. The gut microbiome refers to the whole genome of the resident microbial community in the human intestine. An altered gut microbiome is involved in the development of multiple immune-mediated and inflammatory disorders, especially of inflammatory bowel diseases (IBD), by disrupting the balance between pro-inflammatory and anti-inflammatory/regulatory immune cells [5,6]. Many studies have revealed dysbiosis, alterations in the gut microbiome, in inflammatory and autoimmune skin disorders such as acne, rosacea, atopic dermatitis, and psoriasis [7-10]. However, studies exploring the gut microbiome alterations in patients with HS are scarce in the literature [11-14].

Objectives

In the present study, we hypothesize that the gut microbiome of patients with HS is different from that of healthy people. Therefore, in this study, we aimed (1) to evaluate the gut microbiome of patients with HS, (2) to compare it with healthy subjects, and (3) to evaluate the relationship between fecal microbiome and obesity, smoking status, and treatment condition of HS patients.

Materials and Methods

Study Population

The study was conducted over the period from August 2018 to May 2019 at the Dermatology Department in Hacettepe University and enrolled 30 participants, including 15 patients with HS and 15 age- and sex-matched healthy controls without HS and any other skin diseases. Patients with HS and healthy subjects who were between the ages of 18-65 years, without any systemic antibiotic therapy, probiotics, or prebiotics use in the last 3-months, who were not on a current specific diet (vegan, vegetarian, gluten-free diet), who did not have concomitant systemic inflammatory disease, any infections, previous gastrointestinal tract surgery, and malignancy were included in the study. The diagnosis of HS was based on clinical criteria [15]. The severity of the disease was evaluated by Hurley Stage, modified Sartorius Score, and International Hidradenitis Suppurativa Severity Score System (IHSS4) [16]. Patients and healthy controls were not given dietary restrictions before stool sampling. In order to assess the possible effect of obesity, smoking status, and current treatment on gut microbiome profile, fecal samples of HS patients were stratified by body mass index (BMI), smoking, and current treatment status.

This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Board [24.07.2018, GO 18/62925]. Written informed consent was obtained from all subjects prior to their enrollment.

Fecal Sample Collection

Fecal samples from all participants were collected in sterile containers. Then, all samples were transferred to a freezer within 60 minutes of collection and stored at −80°C until analyzed with New Generation Sequencing (NGS).

DNA Extraction

Total DNA extraction from 30 fecal samples was performed using The Biospeedy® DNA Isolation Kit (Bioeksen R&D Technologies) according to the manufacturer instructions. Feces (200 mg) was transferred to 300 µL of buffer (200 mM Tris-HCl, pH 8.0; 20 mM EDTA; 10% Triton X-100) and 0.1-mm glass bead containing tubes and homogenized at 6000 rpm for 1 min. 0.1 µL lysozyme (200 µg/µL) was added to the sample and incubated at 37°C for 15 minutes. Subsequently, 250 µL lysis buffer (0.5 µg /µl Proteinase K, 5% Tween® 20, 3M Guanidinium thiocyanate, 20 mM Tris-HCl, pH 8.0) was added to the sample and incubated at 70°C for 15 minutes and then 95°C for 5 minutes. After incubation, one volume of isopropanol was mixed with the sample, passed through silica columns by centrifugation, and washed twice with washing buffer (20 mM NaCl, 2 mM Tris-HCl, pH 7.7, 80% v/v ethanol). DNA was eluted with 50 µL 100 mM Tris-HCl (pH) and stored at -20°C until analyzed. Spectrophotometric methods measured the amount and quality of isolated DNA in samples, and their suitability to the next steps was tested. Next molecular processes were performed with DNA with OD260 / OD280 ratio of 1.8-2.0 and OD260 / OD230 ratio of 2.0-2 and at least 10 ng/ul (preferably 50-300 ng / µL) concentrations.

16S rRNA Amplification

The amplification of the V3 and V4-conserved regions of bacterial 16S rRNA were performed by polymerase chain reaction (PCR) using Illumina adapter overhang nucleotide 16S rRNA-specific sequences,
Bioinformatics and Statistical Analyses

The raw sequence data were processed using QIIME2 v2019.1 software. First, the barcode and the primers were trimmed, and unique sequences were identified. Pre-clustering prevented redundancy. UCHIME was used for the removal of chimeras. Next, the sequences were classified using a classifier within QIIME2. The references and taxonomy files were obtained from the QIIME2 database. After picking operational taxonomic units (OTU) at 97% sequence similarity and taxonomy assignments using the QIIME2 and SILVA rDNA database, the OTUs were binned into phylotypes.

Alpha diversity and beta diversity were calculated with QIIME2 v2019.1 software. The alpha diversity is defined as the diversity within a community and was calculated using Shannon, Simpson’s, ACE, Chao, and Faith Phylogenetic diversity indices. The beta diversity is defined as the distance between communities and was calculated by Bray-Curtis dissimilarity and Jaccard distance and represented in a three-dimensional Principal Coordinate Axis on EMPeror. Statistical analyses were performed using Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, United States) and MINITAB 17 software (Minitab Ltd. Co., Coventry, UK).

Results

The Characteristics of Participants

We enrolled 15 patients with HS and 15 age- and sex-matched healthy controls in this study. All subjects were Turkish in origin and coming from exact geographical locations. The characteristics of study groups are shown in Table 1.

Fecal Microbiome Analysis Between HS and Healthy Groups

Community Richness and Diversity

The alpha-diversity of the gut microbiome was significantly lower in HS patients than healthy individuals (Shannon index, P = 0.048). The Simpson, ACE, Chao, and Faith phylodiversity indices of HS patients were lower than those of controls; however, the differences were not statistically significant (P > 0.05) (Figure 1).

The gut microbiome composition in HS patients was significantly distinct from healthy controls. The results of Bray-Curtis and Jaccard Dissimilarity indices showed significantly different clustering of HS patients and healthy subjects based on PERMANOVA statistical analyses (P = 0.01 and P = 0.007, respectively), indicating that the bacterial community structure in HS is different from that in healthy controls (Figure 2).

Overall Taxonomic Analysis of HS Patients and Controls, Distribution at the Phylum Level

The gut microbiome of both HS patients and healthy controls was largely dominated by Firmicutes (relative abundance 92.64% vs. 93.10%), Bacteroidetes (5.35% vs. 4.64%), Actinobacteria (0.95% vs. 1.23%), unclassified Bacteria (0.4% vs. 0.54%), Proteobacteria (0.52% vs. 0.4%) and Verrucomicrobia (0.52% vs. 0.4%). The proportions of rare phyla including Synergistetes, Tenericutes, Fusobacteria, Candidatus_Saccharibacteria, Acidobacteria, Chloroplast, and Cyanobacteria were present at much lower levels. Firmicutes was the most predominant phylum among all relatively abundant dominant taxa in HS and healthy controls. The overall microbial composition of each group at the phylum level is represented in Figure 3. The phylum unclassified Bacteria was significantly reduced (P = 0.032) in the HS group compared to the healthy control, whereas other phyla showed no significant difference.

Overall Taxonomic Analysis of HS Patients and Controls, Distribution at the Genus Level

Lachnospiraceae_unclassified, Ruminococcaceae_unclassified, Clostridiales_unclassified, Roseburia, Gemmiger, One-sample t-test, Mann-Whitney U test, PERMANOVA, and Kruskal-Wallis test were used for statistical significance analysis. Statistical significance was set at P < 0.05.
Table 1. Characteristics of hidradenitis suppurativa patients (N = 15) and healthy individuals (N = 15) included in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HS patients (N = 15)</th>
<th>Healthy controls (N = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / Female (N)</td>
<td>10 / 5</td>
<td>10 / 5</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean ± SD (range)</td>
<td>33.23 ± 12.29 (18-57)</td>
<td>33.23 ± 12.29 (18-57)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>28.63 ± 5.7</td>
<td>24.7 ± 2.37</td>
<td>0.026*</td>
</tr>
<tr>
<td>Healthy weight (N)</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Overweight (N)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Obese (N)</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cigarette pack year, mean ± SD</td>
<td>13.13 ± 11.79</td>
<td>4.93 ± 9.97</td>
<td>0.011*</td>
</tr>
<tr>
<td>Current smoker (N)</td>
<td>13</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Non-smoker (N)</td>
<td>2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Disease onset, years, mean ± SD (range)</td>
<td>24 ± 9.9 (15-48)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Family history (N)</td>
<td>5 / 15</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hurley stage (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Modified Sartorius Score</td>
<td>48.6 ± 33.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IHS4 score, mean ± SD</td>
<td>21.87 ± 15.25</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Mild (N)</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Moderate (N)</td>
<td>4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Severe (N)</td>
<td>11</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Visual Analogue Scale, mean ± SD (range)</td>
<td>7.53 ± 1.76 (5-10)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Medication use (N)</td>
<td>5 / 10</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Systemic retinoids</td>
<td>4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; HS = hidradenitis suppurativa; IHS4 = International hidradenitis suppurativa severity score system; SD = standard deviation; * P < 0.05.

Figure 1. Alpha diversity of the gut microbiome of HS patients and healthy subjects. Shannon index box and whiskers plots showed significantly reduced alpha diversity in HS patients (P = 0.048). HS = hidradenitis suppurativa.
Figure 2. Beta diversity of the gut microbiome of HS patients and healthy subjects. Each data point represents an individual sample. Jaccard Dissimilarity Index showed significantly different microbiome clustering of HS patients and healthy subjects (P = 0.007) presented through principal coordinate Axis 1, indicating that the bacterial community structure in HS is different from that in healthy controls. HS = hidradenitis suppurativa.

Figure 3. Relative abundance of the gut microbiome distribution at the phylum level. The phylum Bacteria_unclassified was significantly reduced (P= 0.032) in the HS group compared to the healthy controls, whereas other phyla showed no significant difference. * P < 0.05 HS = hidradenitis suppurativa.
Coprococcus, Blautia, Ruminococcus2, Fusicatenibacter, Faecalibacterium, Dorea, Firmicutes_unclassified, Dialister, and Ruminococcus were main genera (>1%) in both groups. In HS and control groups, Lachnospiraceae_unclassified (28.85% vs. 27.35%), Ruminococcaceae_unclassified (10.68% vs. 11.54%), Clostridiales_unclassified (7.90% vs. 9.07%), and Roseburia (9.96% vs. 8.66%) were the four commonest genera. Among all genera, the relative abundance of Clostridiales_unclassified, Firmicutes_unclassified, and Fusicatenibacter in HS was significantly lower than in controls (P= 0.005, P= 0.029, and P= 0.046, respectively) (Figure 4).

**Analysis of Fecal Microbiome When Stratified by BMI, Smoking Status, and Treatment of HS Patients**

Shannon and Simpson diversity indices showed no significant differences between non-obese and obese, non-smokers and smokers, and treatment naïve and under treatment groups analyzing alpha-diversity (P= 0.536 and P= 0.281, P=0.076 and P=0.076, P=0.440 and P=0.254, respectively). Fecal microbiome composition evaluated by Bray-Curtis and Jaccard Dissimilarity indices was not significantly different among non-obese and obese, non-smokers and smokers, and treatment naïve and under treatment groups (P=0.656 and P=0.73, P=0.883 and P=0.729, P=0.391 and P=0.648, respectively). Taxonomic analysis at the phylum and the genus level showed no significant taxa alterations among non-obese and obese, non-smokers and smokers, and treatment naïve and under treatment groups.

**Conclusions**

Based on our hypothesis that the gut microbiome of patients with HS is different from healthy people, we conducted a 16S rRNA-based metagenomics analysis of fecal samples in patients with HS and demonstrated a dysbiotic state in HS patients. We showed significantly decreased alpha diversity of gut microbiome in patients with HS, indicating lower bacterial community richness than healthy controls. In addition, bacterial community structure, beta diversity, was significantly different between patients with HS and healthy controls.

Previous studies on gut microbiome alterations in HS patients are summarized in Table 2 [11-14]. Kam et al and McCarthy et al showed decreased alpha diversity in HS patients in line with our results [12,14]. However, the bacterial community structure of HS patients was different from that of healthy people only in McCarthy et al study [14]. When we compared the bacteria distribution at the phylum level, there was no significant difference other than unclassified bacteria phylum between HS and healthy subjects in our study. On the other hand, our results indicated that the abundance of three genera had been significantly reduced in HS patients: unclassified Clostridiales, Fusicatenibacter, and

![Figure 4. Relative abundance of the gut microbiome distribution at the genus level. The relative abundance of three genera: unclassified Clostridiales, unclassified Firmicutes, and Fusicatenibacter in HS was significantly lower than that in controls (P = 0.005, P = 0.029, and P = 0.046, respectively). * P < 0.05 HS = hidradenitis suppurativa.](image)
### Table 2. Gut microbiome studies conducted with HS patient.

<table>
<thead>
<tr>
<th>Study participants</th>
<th>Ethnicity</th>
<th>Current treatment status of participants</th>
<th>Method of the gut microbiome analysis</th>
<th>The minimum time interval between antibiotic usage and sample collection</th>
<th>Alpha-diversity</th>
<th>Beta-diversity</th>
<th>Main findings on the relative abundances of gut bacteria in HS patients in comparison to healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>15 HS vs 15 HC</td>
<td>All Caucasians</td>
<td>4 patients on systemic retinoid and 1 patient on anti-TNF-α therapy</td>
<td>Fecal samples 16S rRNA</td>
<td>3 months</td>
<td>Decreased alpha-diversity in Shannon index No significant results in Simpson, Faith’s phylodiversity, ACE, and Chao indices</td>
<td>Significantly different bacterial compositions in Bray-Curtis and Jaccard Dissimilarity Indices</td>
</tr>
<tr>
<td>Eppinga et al, 2016 [11]</td>
<td>17 HS vs. 33 HC</td>
<td>76% of HS and HC are Caucasians</td>
<td>1 patient on anti-TNF-α therapy</td>
<td>Fecal samples Quantitative PCR</td>
<td>8 weeks</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kam et al, 2021 [12]</td>
<td>3 HS vs. 3 HC</td>
<td>African-American: 3 and Hispanic: 0 in HS group African-American: 2 and Hispanic: 1 in the HC group</td>
<td>Not specified</td>
<td>Fecal samples 16S rRNA</td>
<td>4 weeks</td>
<td>Decreased alpha-diversity in Shannon index No significant results in the number of observed OTUs No significant differences in UniFrac distance matrices</td>
<td>Decreased relative abundance of phylum Firmicutes Increased relative abundance of Bilophila and Holdemania Decreased relative abundance of Lachnobacterium and Veillonella</td>
</tr>
<tr>
<td>Lam et al, 2021 [13]</td>
<td>17 HS vs. 20 HC</td>
<td>13 Caucasians in the HS group and 15 Caucasians in the HC group</td>
<td>1 patient on anti-TNF-α therapy 9 patients on topical therapy</td>
<td>Fecal samples 16S rRNA</td>
<td>8 weeks and 7 days</td>
<td>No significant results in bacterial richness, Shannon and, inverse Simpson Indices No significant differences in Bray-Curtis and Jaccard Dissimilarity Indices</td>
<td>Increased relative abundance of Robinsoniella, Sellimonas, Eggerthella, Flavonifractor, Oscillibacter, Lachnolastrium, and Romboutsia Decreased relative abundance of Parasporobacterium Decreased relative abundance of Christensenellaceae, Lachnospiraceae, and Porphyromonaceae</td>
</tr>
</tbody>
</table>

HC = healthy controls; HS = hidradenitis suppurativa; out = operational taxonomic unit; rRNA = ribosomal ribonucleic acid; TNF = tumor necrosis factor.

Unclassified Firmicutes. Various taxa alterations have been noted in studies conducted with HS patients, and there was no common bacterial taxa alteration between our study and the other study results (Table 2) [11-14]. These differences between study results in taxa distribution could be attributed to ethnic diversity and consequently different dietary habits of the study samples [17].

Eppinga et al investigated the abundance of two species in the gut microbiome of psoriasis and HS patients with and without concomitant inflammatory bowel diseases (IBD): Faecalibacterium prausnitzii and Escherichia coli. The study reported significantly reduced Faecalibacterium prausnitzii in solely psoriasis patients, psoriasis with IBD patients, and IBD patients. In addition, the study showed a significant reduction in the abundance of Faecalibacterium prausnitzii in patients with concomitant IBD and HS. However, there was no significant difference in Faecalibacterium prausnitzii in patients with solely HS.11 Compatibly, the abundance of the
The gut microbiome plays a critical role in human health through the development of immune responses mediated by metabolic products and inflammatory signaling pathways [18]. It has been shown that commensal bacteria produce immunomodulatory metabolites, particularly short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate. These metabolites have anti-inflammatory actions mediated by G-protein coupled receptors and contribute to the epithelial barrier integrity [19]. Short-chain fatty acids producing bacteria induce peripheral T-regulatory cells (Tregs), eliminate the Th17/Th1 response and provide a balance between pro-inflammatory and anti-inflammatory immune cells [6,20-23]. Some bacterial taxa are well-characterized with their anti-inflammatory properties. For example, Firmicutes phylum is known for its anti-inflammatory actions via producing SCFAs [18]. Three genera, unclassified Clostridiales, Fusicatenibacter, and unclassified Firmicutes that were shown to be decreased in our study, belong to Firmicutes phylum. Faecalibacterium prausnitzii and Roseburia species are other well-known anti-inflammatory bacteria and play a critical role in IBD [24,25]. The relative abundance of Faecalibacterium and Roseburia was not different between the gut microbiome of patients with HS and healthy controls. However, decreased abundance of Fusicatenibacter was remarkable in HS patients. Fusicatenibacter saccharivorans is a recently isolated and cultured bacterium and a strain of Clostridium subcluster XIVa that induces Tregs and produces butyrate and other SCFAs [26,27]. A recent study has reported that F. saccharivorans decreased in patients with active ulcerative colitis (UC), and there is a negative correlation between the abundance of Fusicatenibacter saccharivorans and UC activity [28]. Therefore, a lower abundance of unclassified Clostridiales, Fusicatenibacter, and unclassified Firmicutes in the gut microbiome of patients with HS may be a triggering factor for systemic inflammation through decreased SCFA production and dysregulation of inflammatory mechanisms, which lead to a shift toward a pro-inflammatory state.

Seven of 15 HS patients included in our study were obese, and 13 out of 15 patients with HS were current smokers. Obesity is a common comorbidity in patients with HS and is considered a risk factor in the development of HS along with smoking and aberrant regulation of innate immunity [15,29]. Gut microbiome alterations may underlie a common pathophysiological process for HS, obesity, smoking, and aberrant immune response by producing various microbial metabolites and consequent inflammation. Recently, several studies in humans and animal models have shown the gut microbiome impact on obesity, and dysbiosis of the gut microbiota is closely associated with obesity [30-32]. A few studies in the literature show the effect of smoking on the gut microbiome. These studies have found an association between smoking status and gut microbiome composition, which is that the composition of the gut microbiome of smokers is different from that of non-smokers [33-35]. In our study, there were no significant differences neither in diversity nor taxa distribution between the gut microbiome of obese and healthy subjects or the gut microbiome of smokers and non-smokers.

Several limitations of this study should be noted. First, we could not perform a power analysis, and the sample size was small in study subgroups. Larger sample size should be concluded with more significant results in future studies. Second, although we excluded participants using antibiotics, probiotics, prebiotics, and on a specific diet, not following a standard diet among participants may have affected the composition of the gut microbiome. Third, there were five HS patients under treatment during fecal sample collection in our study. We did not find significant differences in diversity and bacteria distribution between patients under and without treatment. Nevertheless, the inclusion of patients with similar treatment status is warranted to understand better the gut microbiome’s role in the pathogenesis of HS.

This study indicated that significant alterations in the gut microbiome of HS patients could play a critical role in the pathogenesis of HS. These findings also provide further insights that the gut–skin axis contributes to the pathogenesis of chronic inflammatory skin disorders. Further investigations are required to explain the connections between the gut microbiome and the pathogenesis of HS. Increased understanding of the pathogenesis of HS will shed light on the new potential therapeutic targets, and novel treatment options such as probiotic and prebiotic supplementation or even fecal microbiome transplantation will arise in the management of this challenging chronic skin disorder.

References


Increased Prevalence of Bipolar Disorders in Hidradenitis Suppurativa: More Than a Striking Co-existence?

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Key words: Hidradenitis suppurativa, bipolar disorders, psychiatric, co-morbidity, co-existence

Introduction: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder of the hair follicle characterized by intense discharge and pain. Recently, HS intrinsic association with neuropsychiatric disorders has become a focus of attention, and bipolar disorder (BD) emerged as a relevant topic for such an association.

Objectives: This study aimed to evaluate BD prevalence among HS patients and present the HS and BD overlap patients demographics, detailed clinical characteristics with a discussion on aggravating factors.

Methods: A retrospective chart review of 247 HS outpatients (Group-1) identified nine patients with BD. The frequency of BD in HS patients is compared to psoriasis patients (Group-2) and controls (Group-3) in age- and gender-matched groups. The demographic and clinical features of the 9 patients revealing HS-BD co-existence were analyzed.

Results: BD (N = 9) was the 7th most common co-morbidity in the HS cohort. The frequency of BD is detected as 3.6% in group 1, 0.7% (N = 1) in group 2, and 0.6% (N = 1) in group 3, respectively. Group 1 demonstrated an increased prevalence of BD compared to other groups (P = 0.001). Of the 9 patients revealing HS and BD co-existence, 66.6% were active smokers, 66.6% were obese and 44.4% had metabolic syndrome.

Conclusions: This study results reveal that the prevalence of BD in HS patients is higher than psoriasis patients and controls. The pathogenetic mechanisms underlying BD and HS co-existence needs to be investigated further.
Introduction

Hidradenitis suppurativa (HS) is a highly painful and extremely destructive, inflammatory skin disease of the hair follicle with substantial negative psychosocial impacts on patients. Many HS patients suffer from psychiatric conditions, such as depression, anxiety, impaired self-esteem, and stigmatization. Therefore, a psychiatric evaluation of HS patients is strongly recommended [1]. Through the evaluation of neuro-psychiatric disorders in HS patients, bipolar disorders (BD) have just begun to attract attention [2,3].

HS and BD are relatively common conditions affecting more than 1% of the population for each condition. The onset of these chronic, fluctuating diseases is typically in young adulthood and both are considered as leading causes of disability among young people [4-6].

A substantial proportion of BD patients report a positive family history for BD connoting the contribution of genetics; however similar to HS, the multifactorial model including gene environment interactions is accepted as the best concept to explain BD etiopathogenesis [7]. Furthermore, numerous associations have been purported between bipolar disorder and other medical co-morbidities including cardiovascular disorders, diabetes and obesity [8-11]. The higher prevalence of these medical co-morbidities in BD is principally explained via three perspectives including the adverse effects of pharmacological treatments, genetic vulnerability, and lifestyle (eg smoking, malnutrition, and sedentary life-style) [4,12].

Population-based studies were conducted to search for an intrinsic relationship between HS and BD with conflicting results [2,3,13]. Some studies reported a remarkably increased prevalence of BD among HS patients; however, others did not confirm such an association. Lithium, one of the most effective treatments for the prevention of both manic and depressive episodes is also acknowledged as an extrinsic factor to exacerbate HS lesions [14]. Additionally, similar to BD, smoking and obesity are strongly linked to HS pathogenesis [4]. BD and HS are complex traits influenced by numerous common genetic variants; however, the existence of a genetic association between HS and BD has not been investigated [15,16].

Objectives

This study aimed to evaluate BD prevalence among HS patients and present the HS and BD overlap patients’ demographics, detailed clinical characteristics with a discussion on aggravating factors.

Methods

The patients diagnosed and followed up in the HS outpatient clinic of Gülhane Training and Research Hospital of the University of Health Sciences between September 2018 and November 2020 were included. The authors conducted a retrospective chart review to extract the variables of interest, including the patients demographic and clinical features (age, gender, age of onset, disease duration, Hurley stage, International Hidradenitis Suppurativa Severity Score System (IHS4), accompanying medical co-morbidities, particularly psychiatric disorders, medications). The patients in this manuscript have given informed consent to publication of their case details.

Besides, two study groups, including age- and gender-matched patients, were enrolled. These groups were composed of psoriasis patients (group-2) and patients admitted with a non-inflammatory skin disease (eg, xerosis, tinea pedis, and localized dermatitis) to the outpatient clinic of the same tertiary center (group-3).

Among the selection of the study population, all of the psoriasis patients received at least one systemic agent, including conventional drugs or biologic agents. Only the cases with missing data were excluded from the overall study population, and no additional specific exclusion criteria were used.

The authors analyzed patients revealing BD and HS co-existence, particularly for possible aggravating factors.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)-2001 Metabolic Syndrome Diagnosis Criteria was implemented to evaluate metabolic syndrome as it is the most cited definition for metabolic syndrome.

Statistical Analysis

Statistical analyses were performed using the Statistics Package for the Social Sciences (SPSS) for Windows version 22.0 (IBM, Armonk, NY, USA). Numerical variables were presented as mean ± SD or median (min-max). Categorical variables were shown by number and percentage. P < 0.05 was considered significant in all comparisons.

This study must recruit 59 individuals for each group to have 80% power with 5% type I error level to detect clinically significant difference of 1% prevalence when the expected value in the control group is 1%.

Results

A total of 247 HS patients (group 1), consisting of 105 females and 142 males, between 14-68 years of age (mean age: 33.48 ± 11.6 years), were eligible for inclusion in the study. The mean disease duration was 7.3 ± 6.9 years (range 0-35). Of 247 patients, 186 (75.3%) and 14 (5.6%) were active and ex-smokers respectively with an average of 12.7 ± 14.3 (range 1-90) pack-year smoking history. The mean body mass index (BMI) was 28.6 ± 6.8 (min-max:14.8-85) and
33.2% (N = 82) of the patient BMI were over 30. The distribution of Hurley staging was as follows: stage I (N = 82, 33.2%), stage II (N = 81, 33.8%), and stage III (N = 84, 34%). Among 15 co-morbidities detected within the current HS cohort, BD was the 7th most common, encountered in 9 (3.6%) patients (Table 1).

The authors reviewed psoriasis patients (group 2, N = 135) and patients without an inflammatory skin disorder (group 3, N = 152) for the presence of BD. Only one patient had BD diagnosis per group 2 (0.7%, N:1/135) and group 3 (0.6%, N:1/152).

The patient in group 2 was a 40-year-old male. He had been diagnosed with psoriasis 9 years ago and BP onset was noted within the following year. His BMI was 33.9 and he had never smoked before. He revealed chronic plaque psoriasis without psoriatic arthritis. His previous medical history was unremarkable. The initial treatment choice for this patient was methotrexate which was replaced by certolizumab pegol injections due to inefficacy. Psoriasis Area Severity Index [PASI] score reduced from the baseline value of 8 to 1.5 on the 6th month of certolizumab pegol treatment.

The dermatological diagnosis of the BD case in the control group was basal cell carcinoma. The prevalence of BD in the HS cohort (3.6%) was 4.5 and 6 times higher than in the psoriasis cohort (0.7%) and controls (0.6%) (P = 0.001 for Group 1-2 and Group 1-3).

Table 2 exhibits the demographic and clinical characteristics of 11 patients with BD. The majority of the patients with BD were male (N=7/11). Similarly, 6/9 of the patients with HS and BP were male. Family history of HS or BD was present in 4/9 (44.4%) of the patients with HS and BD. Totally (88.8%) 8 of the HS patients had moderate to severe HS according to the Hurley stage and IHS4 scores. The median disease duration of HS and BD was as follows, 6 (min-max:4-20, interquartile range [IQR]: 11) and 7 (min-max:2-16, IQR: 10.5) Of the HS patients, 5 were on adalimumab and 4 were on doxycycline. Of nine cases with HS and BD, 4 (44.4%) had concurrent metabolic syndrome. Most frequently used current medications for BD in HS patients were lithium (N = 5/9) and sodium valproate (N = 4/9). Of 9 HS patients, 6 had been prescribed lithium previously, and 3/6 (50%) reported exacerbations under lithium. Because of uncontrolled BD despite multiple treatments, lithium had to be continued in two of these 3 patients who described exacerbations.

Conclusions

In the current study, the prevalence of BD was 3.6 %. BD frequency was significantly higher in the HS cohort than the psoriasis cohort and control patients. Physicians dealing with HS patients are familiar with psychiatric complaints, occasionally leading to anxiety and depression [17-19]. HS substantial burden on quality of life measures has been proposed as the principal causal factor for the association of HS and psychiatric co-morbidities [19,20].

Associations between several endocrinologic, metabolic and rheumatological disorders and HS reveal that HS is more than skin deep [21]. Deciphering the interdisciplinary links is essential for HS optimal management and

<table>
<thead>
<tr>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Psoriasis</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Crohn disease</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Spondyloarthropathy/ arthritis</td>
<td>Pulmoner disease</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Down syndrome</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Familial Mediterranean Fever</td>
<td>Pyoderma gangrenosum</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Chronic cardiac disease</td>
<td>Vitiligo</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Multiple sclerosis</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = number of patients; SD = standard deviation; % percentage of patients.
Table 2 Demographic and clinical characteristics of patients with bipolar disorders in Group 1 (HS patients), Group 2 (psoriasis patients) and Group 3 (control group).

<table>
<thead>
<tr>
<th></th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>P9</th>
<th>P10</th>
<th>P11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45</td>
<td>52</td>
<td>33</td>
<td>43</td>
<td>59</td>
<td>30</td>
<td>40</td>
<td>33</td>
<td>33</td>
<td>40</td>
<td>37</td>
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<tr>
<td>Gender</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Family history HS/psoriasis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Family history BD</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BMI</td>
<td>25,7</td>
<td>36,1</td>
<td>29,2</td>
<td>29,4</td>
<td>30</td>
<td>30.7</td>
<td>37.0</td>
<td>35,4</td>
<td>43.6</td>
<td>23.5</td>
<td>22.3</td>
</tr>
<tr>
<td>NCEP-ATP III MS*</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>* Waist circumference (cm)</td>
<td>87</td>
<td>94</td>
<td>115</td>
<td>98</td>
<td>84</td>
<td>115</td>
<td>135</td>
<td>122</td>
<td>110</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>* Triglyceride (mg/dL)</td>
<td>225</td>
<td>179</td>
<td>430</td>
<td>320</td>
<td>175</td>
<td>391</td>
<td>235</td>
<td>259</td>
<td>194</td>
<td>-</td>
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<tr>
<td>* HDL-c (mg/dL)</td>
<td>30</td>
<td>35</td>
<td>34</td>
<td>32</td>
<td>35</td>
<td>40</td>
<td>40</td>
<td>43</td>
<td>59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>* Blood pressure &gt;130/85 mmHg</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>* Fasting glucose (mg/dL)</td>
<td>89</td>
<td>91</td>
<td>188</td>
<td>103</td>
<td>95</td>
<td>81</td>
<td>121</td>
<td>99</td>
<td>73</td>
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<td>Active smoker</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Hurley stage</td>
<td>6</td>
<td>15</td>
<td>18</td>
<td>11</td>
<td>14</td>
<td>4</td>
<td>9</td>
<td>12</td>
<td>3</td>
<td>Current PASI:1.5 -</td>
<td>-</td>
</tr>
<tr>
<td>IHS4 score</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>20</td>
<td>20</td>
<td>6</td>
<td>5</td>
<td>0,5</td>
<td>12</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Duration of HS/psoriasis (years)</td>
<td>12</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>16</td>
<td>4</td>
<td>15</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Current treatment-HS</td>
<td>Doxy</td>
<td>ADA, 2 years</td>
<td>ADA, 2 years</td>
<td>Doxy, surgery</td>
<td>ADA, 4 years</td>
<td>Doxy</td>
<td>ADA, 6 months</td>
<td>ADA, 6 months</td>
<td>Doxy</td>
<td>Certolizumab pegol</td>
<td>-</td>
</tr>
<tr>
<td>Current treatment-BD</td>
<td>Lithium, sodium valproate, quetiapine, bupropion</td>
<td>Lithium, Ziprasidone hydrochloride</td>
<td>Lithium, quetiapine</td>
<td>Trifluoperazine hydrochloride, Venlafaxine</td>
<td>Lithium, lamotrigine</td>
<td>Sodium valproate, aripiprazole</td>
<td>Lithium, Risperidone</td>
<td>Sodium valproate, fluoxetine</td>
<td>Sodium valproate</td>
<td>Sodium valproate</td>
<td>Lithium</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>-</td>
<td>DM, HL</td>
<td>-</td>
<td>HT, DM, spondylarthritis, FMF</td>
<td>HL, HT glaucoma</td>
<td>-</td>
<td>HT</td>
<td>Hypertriglyceridemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Ada = adalimumab; BD = bipolar disorders; BMI = body mass index; doxy = doxycycline; F = female; M = male; P = patient; P1-P9 = hidradenitis suppurativa; P10 = psoriasis; P11 = basal cell carcinoma

* NCEP-ATP III MS: Presence of at least 3 of the 5 items marked.
determining novel treatment strategies. In this study, the HS patients with BD were analyzed in detail for the presence of common predisposing factors. Of these 9 patients, 4 (44.4%) had metabolic syndrome (Table 2). Three (33.3%) patients were overweight, and 6 (66.6%) patients BMI were over 30. Furthermore, 6 (66.6%) of them were active smokers. These findings suggest the contribution of extrinsic factors to the HS-BD co-existence. Among psychiatric research, genome-wide association studies (GWAS) have introduced interesting perspectives on the intricate relationship of psychiatric disorders with concurrent co-morbidities, especially obesity and metabolic syndrome [22].

On the other hand, more recently, HS and neuropsychiatric disorders’ possible intrinsic relationship has become a focus of attention. Genetic studies point out shared pathogenesis for HS and Alzheimer disease (AD), both revealing mutations within the adjacent parts of the gamma-secretase gene [23]. However, population-based studies do not detect an increased risk of AD in HS patients [24,25]. This is not surprising considering the relatively younger age of HS patients.

BD increased prevalence among HS patients emerged as another relevant topic to search for an intrinsic relationship. For the 9 patients revealing HS-BD co-existence, 4 (44.4%) had a positive family history for HS and 4 (44.4%) had a positive family history for BD. Only two (22.2%) patients reported a positive family history for both BD and HS.

Scarce data exist on the co-existence of HS and BD. Initially, Tzur Bitan et al. reported a sevenfold increase in the prevalence of BD among HS patients (0.7%, 29 of 4,191) compared with controls (0.1%) in a nationwide population-based study [2]. In another large cohort, BD prevalence in HS was 0.6% (9 of 1,411 HS patients) [3]. BD frequency in HS is relatively lower in these two studies compared to the current research [2,3]. On the contrary, a Finnish nationwide registry study indicated a higher figure of 3.1% in HS patients, similar to the current study results [4]. The apparent differences between these studies reveal the requirement of an additional evaluation for the study region baseline characteristics. Studies related to BD in Turkey have exhibited a similar prevalence to those in other countries [26,27]. Turkey is considered one of the countries with the lowest prevalence of mental disorders [28]. Geographic location cannot explain BD increased prevalence in the current study. Instead, it may be related to our department characteristics as a referral center with higher awareness and clinical experience for HS patients.

Lithium effect on HS is possibly patho-physiologically related to acneiform eruption induction [2]. Benhadou et al detected exacerbations in eight of nine HS patients who were prescribed lithium for BD. Lithium was suggested as the potential cause for the initiation and worsening of HS lesions in 25% and 75% of the patients [2]. In the current study, six of nine BD patients with a history of lithium use experienced HS exacerbations. Accordingly, a key question for the physicians encountering HS and BD co-existence is as follows: should lithium be avoided in these cases even in the earliest stages of HS to prevent HS progression? The correct response relies on each patient’s individual features and the interdisciplinary interactions. Considering other treatment options may be more appropriate, if not, indeed required for BD management. However, in the current cohort, three cases never used lithium. Additionally, six cases defined HS onset before or concurrent with BD diagnosis, highlighting additional factors’ contribution.

Some immunological studies have highlighted an increased level of tumor necrosis factor-alpha (TNF)-α, soluble interleukin (IL)-2 receptor, soluble TNF receptor 1 (TNFR1), IL-26 and IL-6 levels in BD, just as HS [2,8,29]. HS is distinguished among other inflammatory skin diseases related to the substantially increased cytokine burden [30]. Thus, the CNS effects of the altered cytokine pattern may be more pronounced compared to other inflammatory skin diseases. Upon study design, to search for the confounding role of chronic inflammation on BD, the authors selected the age and gender-matched controls from psoriasis patients, the prototypic chronic inflammatory skin disease which is also linked to metabolic syndrome and obesity [31]. Moreover, another control group was assigned among outpatients without a chronic inflammatory skin and/or systemic disease. The results of the study pointed out an increased prevalence of BD in only HS patients but not psoriasis patients compared to that of the control group.

The association between the inflammatory cytokines and BD warrants further investigation related to both diagnostic and also possible therapeutic insights. Due to the shared immunologic pathways, a single immunomodulatory drug has the potential to relieve both HS and BD symptoms. While the anhedonia symptoms of the patients with bipolar I/II depression improved significantly under infliximab [32], no clinical improvement was evident in resistant depression with infliximab in two other placebo-controlled clinical trials [33,34]. Even if there is no clinical benefit, a considerable reduction in highly sensitive C-reactive, TNFR1, and nuclear factor-kappa B (NF-kB) proteins were remarkable for bipolar depression [34,35].

Currently, the only FDA-approved treatment for HS is adalimumab [1]. Although the direct efficacy of adalimumab on BD has not been reported, the available data from Crohn disease, rheumatoid arthritis, and ankylosing spondylitis cohorts receiving adalimumab report lower depression scores, improvement in somatic symptoms, and mental scores amelioration [36]. In the current study, 5/9 patients with BD and HS have been taking adalimumab for 6 months.
to 4 years. Authors observations for these 5 patients upon physician-patient interactions can be reported as a remarkable improvement for both diseases during adalimumab treatment, but without any objective assessments for BD. However, attributing all improvements to adalimumab in BD does not seem appropriate as all five patients have continued psychiatric drugs simultaneously for the treatment of BD (Table 2). Additionally, the improvement of underlying disease severity and quality of life measures under adalimumab treatment will undoubtedly affect BD positively.

The current study period comprises the pandemic period. Therefore, the results of the study offered the chance to observe the disease course of COVID-19 in HS patients, apart from revealing the frequency of BD in HS patients. Although the course of COVID-19 in HS patients was not an outcome measure for this study, the authors observations are the line with the findings of the recent report by Dewigne et al and support that the prevalence of COVID-19 is not higher in HS patients, despite the many accompanying medical comorbidities and risk factors in HS [37]. During the period of this study, only 1 patient in our HS study group (N = 247) died in the intensive care unit due to COVID-19. This case had concomitant rheumatoid arthritis and familial Mediterranean fever and was under 6-month certolizumab pegol treatment for HS.

The small sample size and the retrospective nature were the major limitations of the current study. Since our center is a referral tertiary healthcare institution with special HS outpatient clinic, this affects the generalizability of our results. However, from a deductive perspective, we believe that this case series will complement the available nationwide surveys on this relatively novel subject to provide essential insights.

The current retrospective analysis results verify that the prevalence of BD in HS patients is higher than psoriasis patients and controls. Another factor to keep in mind is that the real-life prevalence of BD in HS could be higher than expected due to the underdiagnosis of HS. Different aspects of this co-existence need to be elucidated in the future with an ideal treatment strategy to prevent these patients from lithium-induced exacerbations. A detailed understanding of the common immunologic and possibly genetic alterations in both diseases seems crucial in identifying a targeted therapy or optimal treatment combination in patients with BD and HS.

References


Transepidermal Delivery of Triamcinolone Acetonide or Platelet Rich Plasma Using Either Fractional Carbon Dioxide Laser or Micro-needling in Treatment of Alopecia Areata

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¹ Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Alexandria University, Egypt

Key words: alopecia areata, drug delivery systems, carbon dioxide laser, platelet rich plasma, triamcinolone acetonide

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ABSTRACT

Introduction: Trans-epidermal drug delivery, using “laser-assisted drug delivery”, or micro-needling, are new treatment modalities, that can improve drug penetration into skin in treatment of alopecia areata patients.

Objectives: To evaluate the use of fractional carbon dioxide laser versus micro-needling in trans-epidermal delivery of triamcinolone acetonide and platelet rich plasma in alopecia areata treatment.

Methods: Interventional comparative study carried out on 60 patients, randomly divided into four equal groups. Group I: Fractional Carbon dioxide laser and triamcinolone acetonide. Group II: micro-needling with Dermapen and triamcinolone acetonide. Group III: fractional carbon dioxide laser and platelet-rich plasma. Group IV: micro-needling with Dermapen and platelet-rich plasma. Patients were evaluated clinically, using Severity of Alopecia Tool score and hair regrowth scale, and dermoscopically.

Results: In all treatment groups, there was improvement in the Regrowth scale, with statistical significance between the different groups at fourth (P = 0.001) and last (P = 0.008) visits, with highest, most significant changes in Pen-Steroid group. Comparing Regrowth scale at last visit, results were in...
Introduction

Trans-epidermal drug delivery (TED) depends on using ablative method (CO\(_2\) laser, erbium lasers or ablative radiofrequency), to create vertical channels through the epidermis. This is followed by applying a medication (eg triamcinolone acetonide, platelet rich plasma) that is delivered through these channels into the skin. “Laser-assisted drug delivery” is the specific use of lasers for TED. Micro-needling technique can be used for the same purpose [1].

Objectives

The aim of this study is to evaluate the use of fractional carbon dioxide laser versus micro-needling in trans-epidermal delivery of triamcinolone acetonide and platelet rich plasma in alopecia areata (AA) treatment, clinically and dermoscopically.

Methods

Patients Group

This interventional comparative study was carried out on 60 patients, of either sex, presenting with AA to the Dermatology, Venereology and Andrology outpatient and Hair clinics in the Main University Hospital. The local Ethics Committee approved the study, and all procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000. All patients signed an informed written consent. Assent was obtained from minors, and their parents signed written consents.

The inclusion criteria were patients with AA of both sexes, aged 6-60 years, not responding to treatment (topical and/or systemic) for at least 3 months, and off treatment for at least 1 month, prior to the study. The exclusion criteria [2,3] included AA with spontaneous hair regrowth, active scalp inflammation, other scalp or hair diseases, history of hypertrophic scar or keloid, bleeding disorders, and long-term use of anti-coagulant therapy. Pregnant and lactating females and immunocompromised patients were excluded.

Closed envelope method was used to randomly distribute the patients over the study groups. The study included four groups, 15 patients each:

Group I: Fractional Carbon dioxide laser (CO\(_2\) Laser) and triamcinolone acetonide (TrA; 10mg/ ml) [1,4]:

Fractional CO\(_2\) laser was used in ablative mode, using (ATL-250 laser): 10,600nm CO\(_2\) medical laser system built by Advanced Technology Laser Company, Ltd., Shanghai, China. Scanning mode was used with the following parameters: power of 20 Watts, density of PPI 4 (pulses per inch, i.e. array density), and pulse duration/time on of three milliseconds. One pass was applied to the treated area without gaps between pulses, overlap of about 20% was allowed. Scanning area was set to square shape, ratio 9/9, and size 100%. In smaller patches, dimensions were modifiable. Immediately after the laser pass, TrA solution was dripped on the treated area and spread evenly using the blunt end of syringe.

Group II: Micro-needling with Dermapen and triamcinolone acetonide (TrA; 10mg/ml) [5]:

Dermapen with a 36-needle disposable tip was used, with 2-2.5 mm long needle depth. The speed of the needles’ movement and of the Dermapen movement was adjusted to the patient’s tolerance to pain. The desired end point was minute pinpoint bleeding points or mild erythema. TrA was applied before, during and after performing micro-needling.

Group III: Fractional carbon dioxide laser (CO\(_2\) Laser) and platelet-rich plasma (PRP) [6]:

The same laser parameters as group I were used, followed by application of freshly prepared PRP. PRP was prepared using double-centrifugation protocol, which results in higher platelet concentrations, compared to single centrifugation protocol [7]. For PRP, 10 cc of venous blood were collected from antecubital vein under aseptic conditions, into tubes containing sodium citrate (10:1) as anticoagulant. The initial centrifugation (“soft”/ light spin) was done at 2000 rpm for 5 min. The second centrifugation step (heavy / “hard” spin) was carried out at 4000 rpm for 15 min.

Group IV: Micro-needling with Dermapen and Platelet-rich plasma (PRP) [2,5]:

favor of Dermapen, compared to Carbon dioxide laser for trans-epidermal drug delivery (P = 0.023); and in favor of triamcinolone acetonide, compared to platelet-rich plasma as topical medication (P = 0.015). Dermoscopic signs of improvement included decrease in black dots, and appearance of Upright regrowing hairs (P < 0.001).

Conclusions: Micro-needling and fractional carbon dioxide laser are effective tools for trans-epidermal drug delivery for Alopecia areata treatment. Micro-needling for delivery of Triamcinolone acetonide showed best treatment outcomes. Dermoscopy is highly beneficial in evaluating treatment response in alopecia areata.
Micro-needling was performed as Group II; however, diluted TrA was substituted by PRP.

For all groups:

Each patient received four treatment sessions, spaced three weeks apart [1,2,5], followed by a follow-up visit, four weeks after the last treatment session. Prior to the procedure, topical anesthetic cream, (prilocaine2.5% + lidocaine 2.5%) was applied under occlusion for 15-60 minutes. Patients were instructed not to wash their scalp on the treatment day. No treatments for the alopecia were allowed. Topical post-procedure care, including topical antibiotics, emollient or sunscreen could be used.

On the first visit, thorough history was taken, followed by clinical and trichoscopic evaluation [2-4,8]. Trichoscopic evaluation [9-11] was performed using a DermLite® DL4 (3 Gen), at 10x magnification in polarized mode.

**Patient Evaluation**

The patients were assessed clinically and dermoscopically for signs of hair regrowth at each visit, and at the follow up visit. Using Samsung J5 Pro 13-megapixel camera with F1.7 lens, serial digital photographs (clinical and dermoscopic) of the alopecic patches were taken prior to commencement of the treatment, during the treatment sessions and at the end of the treatment. Two independent investigators evaluated the photographs.

Severity of Alopecia Tool (SALT) score at baseline, at each visit, and at end of study, and hair regrowth scale, were used to calculate treatment response [2,8]. Global assessment score [8] was used to assess the overall improvement, taking into account extent and density of regrowth by SALT score: A0 = no change or further loss, A1 = 1-24% regrowth, A2 = 25-49% regrowth, A3 = 50-74% regrowth, A4 = 75-99% regrowth, and A5 = 100% regrowth. According to the Regrowth scale (RGS), the degree of clinical improvement was evaluated according to a 6-point semi-quantitative score: RGS 0 (re-growth <10%), RGS1 (re-growth 11%-25%), RGS2 (re-growth 26%-50%), RGS3 (re-growth 51%-75%), RGS4 (re-growth ≥75%), and RGS5 (re-growth =100%) [12].

Any side effects like atrophy and telangiectasia were observed, clinically and dermoscopically. Patient satisfaction with results of the procedure was graded as satisfied, fair, and unsatisfied. Pain during procedure was graded as: no pain - mild -moderate -severe- pain as bad as it could be [13].

**Statistical Analysis**

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (IBM Corp). Significance of obtained results was judged at 5% level.

**Results**

**Demographic Data (Table 1)**

Table (1) represents different demographic data and patients details, with no significant difference between all groups. There was no significant difference between the studied groups as regards the Baseline Hair loss, using SALT score [8,9].

**Baseline and Follow-up SALT Scores**

There was no significant difference in SALT score at baseline between the 4 groups.

However, SALT score at last follow-up visit showed statistically significant difference between the different groups (P = 0.005). Eighty percent of patients in Pen-Steroid group improved to SALT S0 (no hair loss), compared to only 40% of patients in CO2-Steroid and Pen-Steroid groups, and only 13.3% in the CO2-PRP group. Pen-Steroid group showed significantly higher improvement compared to CO2-PRP group (P = 0.001).

**Rate of Hair Regrowth (Figures 1-5)**

Over subsequent visits, in all treatment groups, there was a shift in the RGS towards higher scores with improved hair regrowth percentages. However, this improvement showed statistical significance between the different treatment groups only at fourth (P = 0.001) and fifth (P = 0.008) visits. At fourth visit, Pen-Steroid group showed maximum improvement with 53.3% of patients scoring RGS4, followed by Pen-PRP group (40% of patients), then CO2-Steroid group (33.3% RGS4+5), and finally CO2-PRP group with only 13.3% of patients. The difference between Pen-Steroid group and CO2-PRP group was significant (P = 0.003). At the final follow up visit, Pen-Steroid group showed maximum improvement with 80% of patients scoring RGS5, followed by Pen-PRP and CO2-Steroid group (40% of patients), and finally CO2-PRP group with 13.3% of patients. The difference between Pen-Steroid group and CO2-PRP group was statistically significant (P < 0.001).

**Hair Regrowth Score (RGS) at the End of Study**

Improvements in RGS at the end of study, were in favor of using Dermapen for TED (mean RGS 3.93 ± 1.66), compared to CO2 laser (mean RGS 3.13 ± 1.68) , with P = 0.023. Moreover, higher RGS were obtained with TrA as topical medication (mean RGS 4.0 ± 1.53), compared to PRP (mean RGS 3.07 ± 1.76), with P = 0.015.

**Dermoscopic Evaluation (Table 2; Figures 6-8)**

At baseline, most common dermoscopic findings were black dots, in 65% of patients, yellow dots and white dots in 45%
Yellow dots were present at baseline in all groups, and decreased with treatment, but without statistical significance. The decrease in white dots at end of treatment was significantly better in Pen-steroid group compared to the other three groups (P = 0.002). White dots disappeared in 53.3% of affected patients in Pen-steroid group (P = 0.008), compared to only 13.3% in CO₂-PRP and Pen-PRP groups, and none of the affected patients in the CO₂-Steroid group.

Vellus hairs showed no statistically significant difference in occurrence, along sessions.

Upright regrowing hairs were the most consistent feature to indicate hair regrowth. It started to appear after the first treatment session, in most patients in all 4 groups.

Table 1. Comparison between the four studied groups according to demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Steroid CO₂ (N = 15)</th>
<th>Steroid Pen (N = 15)</th>
<th>PRP CO₂ (N = 15)</th>
<th>PRP Pen (N = 15)</th>
<th>Test of Significance</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 40.0</td>
<td>9 60.0</td>
<td>6 40.0</td>
<td>10 66.7</td>
<td>χ²=3.404</td>
<td>0.333</td>
</tr>
<tr>
<td>Female</td>
<td>9 60.0</td>
<td>6 40.0</td>
<td>9 60.0</td>
<td>5 33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>5 33.3</td>
<td>2 13.3</td>
<td>2 13.3</td>
<td>3 20.0</td>
<td>χ²=10.849</td>
<td>0.075</td>
</tr>
<tr>
<td>15 – 30</td>
<td>8 53.3</td>
<td>6 40.0</td>
<td>7 46.7</td>
<td>2 13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30</td>
<td>2 13.3</td>
<td>7 46.7</td>
<td>6 40.0</td>
<td>10 66.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 Y</td>
<td>7 46.7</td>
<td>9 60.0</td>
<td>6 40.0</td>
<td>9 60.0</td>
<td>χ²=1.802</td>
<td>0.614</td>
</tr>
<tr>
<td>≥2 Y</td>
<td>8 53.3</td>
<td>6 40.0</td>
<td>9 60.0</td>
<td>6 40.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present episode (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>8 53.3</td>
<td>6 40.0</td>
<td>7 46.7</td>
<td>12 80.0</td>
<td>χ²=8.192</td>
<td>0.135</td>
</tr>
<tr>
<td>6 - 1Y</td>
<td>7 46.7</td>
<td>9 60.0</td>
<td>7 46.7</td>
<td>3 20.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 Y</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>1 6.7</td>
<td>0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First attack</td>
<td>7 46.7</td>
<td>6 40.0</td>
<td>5 33.3</td>
<td>6 40.0</td>
<td>χ²=0.556</td>
<td>0.907</td>
</tr>
<tr>
<td>Recurrent</td>
<td>8 53.3</td>
<td>9 60.0</td>
<td>10 66.7</td>
<td>9 60.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of AA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patchy</td>
<td>11 73.3</td>
<td>14 93.3</td>
<td>11 73.3</td>
<td>13 86.7</td>
<td>χ²=10.065</td>
<td>0.214</td>
</tr>
<tr>
<td>Ophiasis</td>
<td>3 20.0</td>
<td>0 0.0</td>
<td>2 13.3</td>
<td>0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotalis</td>
<td>0 0.0</td>
<td>1 6.7</td>
<td>2 13.3</td>
<td>2 13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Universalis</td>
<td>1 6.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>9 60.0</td>
<td>9 60.0</td>
<td>8 53.3</td>
<td>11 73.3</td>
<td>χ²=1.340</td>
<td>0.720</td>
</tr>
<tr>
<td>Positive</td>
<td>6 40.0</td>
<td>6 40.0</td>
<td>7 46.7</td>
<td>4 26.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair loss (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max.</td>
<td>1.0 – 100.0</td>
<td>1.0 – 80.0</td>
<td>2.0 – 80.0</td>
<td>2.0 – 80.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>12.80 ± 24.65</td>
<td>11.47 ± 19.50</td>
<td>16.60 ± 25.99</td>
<td>13.53 ± 20.53</td>
<td></td>
<td>0.802</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.0</td>
<td>4.0</td>
<td>7.0</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H = H for Kruskal Wallis test; IQR = Inter quartile range; MC = Monte Carlo.
hairs, which was significantly higher than only 13.3% of patients in \( \text{CO}_2 \)-PRP group (\( P = 0.008 \)). Also, patients who showed pig tail hairs in Pen-PRP group where significantly more compared to \( \text{CO}_2 \)-PRP group (53.3% versus 13.3%, \( P = 0.020 \)).

The study procedure caused no complications that could be observed by dermoscopy. However, telangiectasia and areas of fibrosis, due to previous intralesional steroid injection, could be visualized dermoscopically.

with a statistically significant increase in all study groups (\( P < 0.001 \)).

Terminal hairs, also started to appear after first treatment session, indicating hair regrowth. There was statistically significant rise from baseline to follow up, in all treatment groups (\( P < 0.001 \) in \( \text{CO}_2 \)-Steroid, Pen-Steroid and Pen-PRP groups; \( P = 0.002 \) in \( \text{CO}_2 \)-PRP group).

Pig tail hairs appeared transiently in the course of treatment. In Pen-Steroid group 60% of patients showed pig tail hairs, which was significantly higher than only 13.3% of patients in \( \text{CO}_2 \)-PRP group (\( P = 0.008 \)). Also, patients who showed pig tail hairs in Pen-PRP group where significantly more compared to \( \text{CO}_2 \)-PRP group (53.3% versus 13.3%, \( P = 0.020 \)).

The study procedure caused no complications that could be observed by dermoscopy. However, telangiectasia and areas of fibrosis, due to previous intralesional steroid injection, could be visualized dermoscopically.
Responders were those with hair regrowth ≥ 75% (i.e., RGS 4/ global assessment score A4) [14].

Relation Between Clinical Response and Dermoscopic Features at Baseline (Table 6)

Amongst all 60 patients, presence of black dots at baseline, could not indicate response to treatment. However, presence of Exclamation mark hairs at baseline was significantly related to response ($P = 0.024$), where it was present in 48.7% of responder patients, compared to only 19% of non-responder ones. Yellow dots were significantly related to poor response to treatment ($P = 0.003$), present in 71.4% of non-responder patients at baseline, compared to only 30.8% of responder ones. White dots and vellus hairs were represented insignificantly among responder patients and non-responder ones at baseline.

Onset of Dermoscopic Improvement

Most patients across all treatment groups showed first signs of dermoscopic improvement after first treatment session. Out of the 30 patients receiving TrA, 86.7% showed dermoscopic improvement after first treatment session, compared to 80% of the 30 patients receiving PRP, without statistical significance. The number of patients in Dermapen groups, who showed dermoscopic improvement after first treatment session, was significantly higher than in $CO_2$ groups ($P = 0.010$). This indicates that

**Figure 3.** Pen-PRP group. (A) At base line. (B) At 3rd visit. (C) At 4th visit. (D) At last follow-up visit with complete hair regrowth (100%), hair regrowth scale score 5.
significantly higher (P = 0.046), than CO\textsubscript{2} groups (80.0\% versus 56.7\%).

Relation Between Onset of Dermoscopic and Clinical Improvement
Across all 60 patients included in the study, 82\% who showed dermoscopic improvement after first session also showed clinical hair regrowth after first session (statistically significant).

Dermapen might show faster improvement, compared to fractional CO\textsubscript{2}.

Onset of Hair Growth Clinically
Seventy percent of patients in Steroid groups started to show hair regrowth after first treatment session versus 66.7\% in PRP groups, without statistical significance. The number of patients in Dermapen group, who started to show hair regrowth after first treatment session, was significantly higher (P = 0.046), than CO\textsubscript{2} groups (80.0\% versus 56.7\%).

Relation Between Onset of Dermoscopic and Clinical Improvement
Across all 60 patients included in the study, 82\% who showed dermoscopic improvement after first session also showed clinical hair regrowth after first session (statistically significant).
Table 2. Agreement (sensitivity, specificity and accuracy) for Exclamation mark hairs and Yellow Dots.

<table>
<thead>
<tr>
<th></th>
<th>Non responders (n = 21)</th>
<th>Responders (n = 39)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclamation mark hairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>20</td>
<td>48.72</td>
<td>80.95</td>
<td>82.61</td>
<td>45.95</td>
<td>60.0</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>19</td>
<td>19.0</td>
<td>48.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow Dots</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>27</td>
<td>30.77</td>
<td>28.57</td>
<td>44.44</td>
<td>18.18</td>
<td>30.0</td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>12</td>
<td>71.4</td>
<td>30.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PPV: Positive predictive value  
NPV: Negative predictive value

Figure 6. Pen-Steroid group: Black dots and Exclamation mark hairs. (A) At baseline (†), (B) Disappearing at 4th follow up visit (†), that features mainly upright regrowing and terminal hairs.  
† Black dot  
** Exclamation mark hairs

Figure 7. Pen-PRP group: Black dots and Exclamation mark hairs. (A) At baseline (†), (B) Significant decrease at 4th follow up visit (†), with appearance of upright regrowing and terminal hairs.  
† Black dot  
** Exclamation mark hairs  
|| Upright regrowing
Nevertheless, dermoscopic improvement can herald clinical hair growth. Out of the 22/30 patients in CO₂ groups who showed dermoscopic improvement after first session, 3 started to show clinical hair regrowth after second session and 2 after third session. In Dermapen groups, among the 28 patients who showed dermoscopic improvement after first session, clinical hair regrowth was delayed after second session in 4 patients. Clinical hair regrowth was also delayed to after the second treatment session in four patients in the PRP group. Out of the 26 patients in the Steroid groups who showed dermoscopic improvement after first session, 3 patients showed clinical improvement after the second session and 2 after the third session.

Relation Between Hair Regrowth and Different Parameters

There was no significant correlation between final hair regrowth and patients age, Family history and site of AA patches, in all study groups. Only in CO₂-Steroid group, Hair regrowth at end of treatment, was significantly higher in patients with first attack of alopecia (100 %), compared to patients who had recurrent disease (65 %) (P = 0.031). In CO₂-Steroid, Pen-Steroid, and Pen-PRP groups there was a negative correlation between the total duration of disease and overall hair regrowth. However, this correlation was significant only in CO₂-Steroid (rs = –0.678, P = 0.005) and Pen-PRP (rs = –0.593, p = 0.020) groups. The shorter the duration of the current episode of alopecia, the higher the hair regrowth. This negative correlation was significant only in Pen-PRP group (rs = –0.702, P = 0.004). Patients without body hair affection scored higher hair regrowth rates, in all groups. This negative correlation was statistically significant only in the Pen-PRP group (rs = –0.702, P = 0.004). Patients without body hair affection scored higher hair regrowth rates, in all groups. This negative correlation was statistically significant only in the Pen-PRP group (rs = –0.702, P = 0.004). Although not statistically significant, the less the hair loss at baseline, the better the improvement at end of treatment. This was the case in all the groups, with the exception of the Pen-Steroid one. Hair regrowth, at one month follow up, was higher in patients with patchy hair loss. This was significant in Pen-Steroid (P = 0.021) and Pen-PRP (P = 0.022) groups.

![Figure 8. CO₂-Steroid group: Yellow dots, few vellus hairs and black dots. (A) At baseline. (B)Disappearing at last follow up visit, with appearance of pigtail, upright regrowing and terminal hairs.](image-url)
Side Effects and Patient Satisfaction

Most patients were satisfied by the results, with no statistical significance between the four study groups (CO₂-steroid 86.7%, CO₂-PRP 73.3%, CO₂-Steroid and Pen-Steroid 80%).

Unlike intralesional steroid injection, no atrophy or telangiectasia were observed. Pain during the procedures, was appreciated as more tolerable compared to injection, in patients who experienced intralesional steroid or PRP injection before. In CO₂ groups, the patients expressed their discomfort as related to heat generated from laser procedure.

No major complications, including secondary infection, ulceration or scarring, occurred in any patient.

Conclusions

A main challenge in AA treatment is directing therapies to the hair follicle. Stratum corneum forms a barrier to topical drug penetration, especially hydrophilic and large molecule drugs [15]. Fractional lasers [4] and micro-needling devices may be used deliver drugs to deeper skin layers [16], by creating small channels through the stratum corneum to the dermis–microscopic treatment zones (MTZ) for ablative fractional lasers, and physical puncturing in micro-needling [17,18].

PRP is thought to release growth factors, cytokines, and proteins, from alpha granules, hence stimulating folliculo-genesis and anagen phase [19]. One limitation in evaluating PRP efficacy for AA is lack of standardized protocols [20]. Therefore, vertical uniform channels from skin surface into the dermis, may promote uniform placement of PRP in the dermis and eliminate injection-associated pain [21]. TED can also be used for TrA for the same purposes, with additional advantage of reducing incidence of skin atrophy [4]. This was in accordance with our study, where atrophy and telangiectasia were not observed.

RGS at end of the study were in favor of using Dermapen, compared to CO₂ for TED (P = 0.023). A possible explanation may be occurrence of border of carbonization surrounded by coagulated tissue around the MTZ of fractional CO₂ laser, which may partially hinder drug penetration [22]. On the other hand, dermapen creates transient aqueous microchannels in the stratum corneum, allowing drug permeation by passive diffusion [23]. Moreover, size of dermapen microchannels are in the range of microns, whereas the macromolecules delivered are usually nanometers in size [24]. Also, drugs are applied prior, during and after micro-needling, that is more efficacious in drug delivery, compared to spreading the drug only after laser procedure [25].

Trichoscopy can be used in the diagnosis and monitoring of treatment in AA [26,27]. Appearance of new Short vellus hair as sign of improvement in some studies [26,28] may actually correspond to the upright regrowing hairs, that were the most consistent features of hair regrowth in our study, as the differentiation between both may be difficult [29]. Exclamation mark hairs and black dots decreased significantly with treatment. Yellow dots decreased mildly, but without statistical significance. This was in accordance with a study by Ganjoo and Thappa [26], indicating that exclamation mark hairs, and black dots are markers of disease activity, and are the first parameters to change in response to therapy, whereas yellow dots were the least responsive [26]. Trichoscopy is useful in identification of early atrophy and telangiectasia in patients treated with TrA injections. This allowed avoiding reinjection in these areas [26].

As with our study, changes in the dermoscopic findings as well as hair RGS were observed from the first follow up [30].

Hence, from the present study it can be concluded that, micro-needling and fractional CO₂ laser can be effectively used for TED for AA treatment, and that trichoscopy can be used in AA for evaluation of treatment response.

References


Introduction: Hidradenitis suppurativa (HS) is a chronic, disabling skin disorder which is characterized by recurrent attacks of nodule, abscess, sinus tract formation and scarring. Oral/topical antibiotics, oral retinoids and TNF-alpha inhibitors are used for the treatment of HS.

Objectives: In the present study, we aimed to determine the prevalence of coronavirus disease 2019 (COVID-19) real-time polymerase chain reaction (real-time PCR) positivity and the presence of COVID-19 related symptoms in relation to the age, gender, body mass index, disease duration, treatment used for HS, treatment duration and smoking.

Methods: We conducted a comparative, cross-sectional study of 178 patients diagnosed with HS in a referral hospital. Age, gender, smoking status, body mass index, treatment modalities used for HS, the presence of COVID-19 related symptoms, history of close contact to a person with COVID-19 and COVID-19 real time-PCR results were determined by a telephone questionnaire.

Results: Sixty-three patients were female, whereas 115 patients were male. During COVID-19 pandemic, 94 out of 178 patients had COVID-19 related symptoms; COVID-19 real time-PCR test was performed in 109 (61.2%) patients. Thirty (27.5%) cases tested positive for COVID-19 whereas 79 (72.5%) tested negative.
Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory, debilitating skin disorder characterized by painful, deep-seated nodules and abscesses, draining sinus tracts and cicatrisation [1]. The disease is more likely to be seen in the intertriginous areas of the body including groin, gluteal area, axillae and inframammary region [1]. HS is staged according to the type, extent and severity of the skin lesions [2]. Single or multiple nodules or abscesses without sinus tracts and cicatrix formation refer to Hurley stage 1; recurrent nodules or abscesses with limited sinus tract formation and scarring refers to Hurley stage 2; whereas stage 3 disease is characterized by diffuse involvement of the affected area by nodules/abscesses, multiple interconnected sinus tracts and cicatrisation [2].

Genetic, environmental, endocrinologic, bacterial and host defense related immunologic factors as well as obesity, smoking have all been implicated in the etiology of HS [3]. Depression, inflammatory bowel disease, spondyloarthropathy, diabetes mellitus, hyperlipidemia and metabolic syndrome are among the common associated comorbidities in HS patients [4]. Low self-confidence, sexual dysfunction, impairment of daily functioning, chronic anxiety and depression all lead to poor life quality for HS patients [5,6].

In the early stages of the disease characterized by only a few nodules or abscess, only systemic antibiotics in combination with topical antibiotics or intralesional corticosteroids, are usually enough to control disease activity [7,8]. However, advanced stages require both surgical intervention and systemic treatment modalities. Tumor necrosis factor-alpha (TNF-α) inhibitors (especially adalimumab and infliximab) are the much-preferred agents used in the treatment of advanced stage HS, in combination with topical and systemic antibiotics [9].

During coronavirus disease 2019 (COVID-19) pandemic, the safety of biologic agents is one of the most frequently investigated issues in dermatology practice. The use of antibiotics and TNF-α inhibitors in the patients with HS does not seem to increase the risk for COVID-19 [10].

Objectives

In our study, we aimed to investigate the prevalence of COVID-19 real-time polymerase chain reaction (real time-PCR) positivity and the presence of COVID-19 related symptoms in relation to the age, gender, body mass index (BMI), smoking status, accompanying systemic diseases, disease duration and different treatment modalities used for HS.

Methods

We conducted a cross-sectional, descriptive study of 178 HS patients who were followed up in our dermatology outpatient clinic. All 178 participants were clinically diagnosed with HS and further receiving various treatment modalities according to disease stage in our center’s chronic dermatologic illnesses outpatient clinic between January 2018 and September 2021. Only patients who were under active-continuous treatment for HS during COVID-19 pandemic, were included. Local ethics committee approval was obtained for the present study (the date, project number, decision number: September 7, 2021, GO 21/934, 2021/14-66). An oral questionnaire composed of 15 questions related to the demographic data, HS disease and COVID-19, was formed (Supplementary File 1). The answers were obtained via a telephone survey and an oral informed consent was taken from all the patients before the start of the survey. The accuracy of questions related to COVID-19 status of the participants, characteristics of treatment given for HS and treatment duration, was also verified from the medical data records.

IBM SPSS for Windows Version 20.0 was used for the statistical analysis. Numerical variables were shown as mean ± standard deviation (range: minimum-maximum), whereas categorical variables were given as percentages and frequencies. Shapiro-Wilk test was used to determine if the numerical variables are distributed normally. Fisher’s exact test or Chi-Square test was used to compare the differences between patients receiving various different modalities for HS (divided into 4 groups as oral antibiotics ± topical antibiotics, oral retinoids ± topical antibiotics, TNF-α inhibitors ± oral/topical antibiotics and only topical antibiotics). Logistic regression analyses (in which age, gender, BMI, the presence of any other systemic disease and smoking were included as independent variables) were also performed taking the presence of COVID-19 symptoms and COVID-19 real time-PCR results (positive or negative) as the dependent variables. P values less than 0.05 were considered statistically significant.

Conclusions: Patients having COVID-19 related symptoms were shown to have statistically significantly higher mean age compared to the ones who did not have any symptoms (P = 0.031). No statistically significant relationship was found COVID-19 real time-PCR positivity and the type of treatment administered for HS when categorized as tumor necrosis factor-alpha inhibitor, oral retinoid, topical antibiotic and oral antibiotic group (P > 0.05).
Results

A total number of 178 patients were included in the study. The mean age was 35.69 ± 11.21 years (range:16-61). Sixty-three (35.4%) patients were female, whereas 115 (64.6%) patients were male. Fifty-two (29.2%) patients had Hurley stage 1 disease, 52 (29.2%) patients had Hurley stage 2 disease whereas 74 (41.6%) had stage 3 disease. The mean BMI was 27.55 ±3.30 kg/m² (range:17.09-43.25); one (0.6%) patient had a BMI of <18.5 kg/m² (underweight); 31 (17.4%) patients had a BMI in 18.5 to 24.9 kg/m² range (optimal). One hundred ten (61.8%) out of 178 cases were determined to fall within the overweight category (a BMI of 25-29.9 kg/m²) whereas 36 (20.2%) patients were within the obese category (a BMI of >30 kg/m²). One hundred nine out of 178 patients were current smokers, the mean pack-years of smoking was 21.06 ± 14.12 pack-years (range: 3-80). The mean duration of treatment for HS was 18.37 ± 18.90 months (1-108) whereas the average duration of the disease was 119.38 ± 91.97 months (2-552).

Forty-eight (27%) cases were on oral antibiotics (doxycycline, clindamycin and rifampicin, only clindamycin, tetracycline) treatment either alone or combination with topical treatment modalities. Thirty (16.9%) patients were on oral retinoid (isotretinoin or acitretin) treatment whereas 85 (47.8%) were using TNF-α inhibitors either alone or with oral/topical antibiotics. Out of 85 patients from anti-TNF-α group, 9 (10.8 %) patients were under infliximab treatment, whereas 76 (89.41%) were under adalimumab treatment. Patients with stage 2 and 3 HS were additionally using colchicine. Out of 178 cases, 75 (42.1%) patients had at least one systemic disease. Nineteen (10.7%) patients had rheumatologic illnesses (most common ones being Familial Mediterranean Fever, Behçet disease and ankylosing spondylitis); 22 (12.4%) patients had cardiovascular diseases most frequently being hypertension, coronary artery disease and heart failure. Five (2.8%) case presented with nephrologic diseases whereas five other (2.8%) patients had prior history of malignancy. Endocrinologic disorders such as diabetes mellitus, hypothyroidism and hyperlipidemia were seen in 33 (18.5%) cases, whereas respiratory diseases (most commonly asthma, allergic rhinitis) were present in 11 (6.2%) patients.

During COVID-19 pandemic, 94 (52.8%) out of 178 patients had COVID-19 related symptoms such as fever, anosmia, ageusia, malaise, sore throat, dry cough, diarrhea and myalgia. COVID-19 real time-PCR test was performed in one hundred nine (61.2%) out of 178 patients. Thirty (27.5%) cases tested positive for COVID-19 whereas 79 (72.5%) tested negative. Forty-seven (26.4%) cases had a history of close contact to someone with a confirmed diagnosis of COVID-19. Of 109 patients with COVID-19 real-time PCR test, 30 (27.5%) had positive test result whereas 79 (72.5%) were tested negative. The average age of patients with positive real-time PCR was statistically significantly higher compared to the patients with negative result (p=0.007) (Table 1). There was no statistically significant relationship between gender versus COVID-19 real-time PCR positivity (P = 0.275) and BMI vs COVID-19 real-time PCR positivity (P = 0.873) (Table 1). There was no statistically significant difference in COVID-19 real-time PCR positivity between smokers and non-smokers (P = 0.111) (Table 2). There was no statistically significant relationship between the mean pack-years of smoking of patients who tested positive and negative for COVID-19 (P = 0.222) (Table 2). We found a statistically significant relationship between COVID-19 real-time PCR results and the mean disease duration for HS (P = 0.031) (Table 3). The patients with positive real-time PCR results have a higher mean disease duration compared to the ones with negative COVID-19 real-time PCR results. However, no statistically significant relationship was found between the positive results of COVID-19 real-time PCR and the mean duration of treatment for HS (P = 0.716) (Table 3).

Table 1: Covid-19 Real Time-PCR results in relation to the age, gender and body-mass index.

<table>
<thead>
<tr>
<th>COVID-19 real time-PCR results</th>
<th>Number of patients (n)</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Body-mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Negative</td>
<td>79</td>
<td>35.65</td>
<td>9.94</td>
<td>17</td>
</tr>
<tr>
<td>Positive</td>
<td>30</td>
<td>42.07</td>
<td>11.75</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>37.41</td>
<td>10.80</td>
<td>17</td>
</tr>
</tbody>
</table>

SD = standard deviation.

The average age of patients with positive COVID real time-PCR was statistically significantly higher compared to the patients with negative result (P < 0.007). There was no statistically significant relationship between the gender vs COVID-19 real time-PCR results (P = 0.275). Additionally, there was also no statistically significant relationship between the body-mass index versus COVID-19 real time-PCR results (P = 0.873).
categories as TNF-α inhibitors ± oral/topical antibiotics and others (P = 0.248). In all patients, with a confirmed diagnosis of COVID-19; anti-TNF-α treatment was immediately suspended until full recovery from the disease. Lastly, there was no statistically significant relationship between COVID-19 real-time PCR results and the presence of previous malignancy history; respiratory, cardiovascular,

<table>
<thead>
<tr>
<th>Covid-19 Real Time-PCR Results</th>
<th>Number of patients</th>
<th>Smoking status</th>
<th>Pack-years of smoking (among smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-smoker N (%)</td>
<td>Smoker N (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>79</td>
<td>24 (63.2)</td>
<td>55 (77.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>30</td>
<td>14 (36.8)</td>
<td>16 (22.5)</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>38 (100)</td>
<td>71 (100)</td>
</tr>
</tbody>
</table>

There was no statistically significant difference in COVID-19 real-time PCR positivity between smokers and non-smokers (P = 0.111). Among smokers, no statistically significant relationship was found between the mean pack-years of smoking of patients who tested positive and negative for COVID-19 (P = 0.222).

<table>
<thead>
<tr>
<th>Covid-19 Real Time-PCR Results</th>
<th>Number of patients</th>
<th>Smoking status</th>
<th>Pack-years of smoking (among smokers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-smoker N (%)</td>
<td>Smoker N (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>20 (74.1)</td>
<td>15 (78.9)</td>
<td>35 (67)</td>
</tr>
<tr>
<td>Positive</td>
<td>7 (25.9)</td>
<td>4 (21.1)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (100)</td>
<td>19 (100)</td>
<td>52 (100)</td>
</tr>
</tbody>
</table>

No statistically significant relationship was found between COVID-19 real-time PCR positivity and the type of treatment administered for HS when the treatment modalities are divided into four categories as oral antibiotics ± topical antibiotics, oral retinoids ± topical antibiotics, TNF-α inhibitors ± oral/topical antibiotics and only topical antibiotics (P = 0.657) (Table 4 and Figure 1) or divided into two categories as TNF-α inhibitors ± oral/topical antibiotics and others (P = 0.248). In all patients, with a confirmed diagnosis of COVID-19; anti-TNF-α treatment was immediately suspended until full recovery from the disease. Lastly, there was no statistically significant relationship between COVID-19 real-time PCR results and the presence of previous malignancy history; respiratory, cardiovascular,
significantly higher pack-years of smoking compared to the ones with no symptoms (P = 0.024) (Figure 4).

As expected, there seems to be a statistically significant relationship between the presence of COVID-19 symptoms and COVID-19 RT-PCR positivity (P < 0.001) (Table 5). Of 109 patients who were tested for COVID-19, 75 (68.8 %) had COVID-19 related symptoms; 30 (40%) cases out of 75 cases with COVID-19 related symptoms, were tested positive for COVID. Thirty-four patients who did not demonstrate any symptoms still gave COVID-19 PCR test, were all tested negative. Of 109 patients who were tested for COVID-19, 43 (39.45 %) had close contact to someone with a confirmed diagnosis of COVID-19; whereas 66 (60.55%) did not have any close contact. Twenty-seven (62.8%) cases out of 43 with close contact to a person diagnosed with COVID-19 had positive RT-PCR result. We found a statistically significant relationship between the history of close contact to someone with a confirmed COVID-19 diagnosis and COVID-19 RT-PCR positivity (P < 0.001) (Table 5). No patient was hospitalized for severe COVID-19 infection.

Patients having COVID-19 related symptoms were shown to have statistically significantly higher mean age compared to the ones who did not have any symptoms (P = 0.031). The percentage of patients with COVID-19 related symptoms according to the treatment type was shown in Figure 2. We found no statistically significant relationship between the presence of COVID-19 symptoms and the gender (P = 0.241), BMI (P = 0.472), cigarette smoking (P = 0.272), treatment duration (P = 0.353), disease duration (P = 0.850) and given treatment type when grouped as oral antibiotics± topical antibiotics, oral retinoids, TNF-α inhibitors ± oral/topical antibiotics, colchicine and topical antibiotics (P = 0.124). Patients with cardiovascular disease were shown to present with COVID-19 related symptoms compared to the ones with no accompanying cardiovascular disease (P = 0.035). Additionally, patients who had at least one systemic disease (classified as respiratory, nephrologic, cardiovascular, rheumatologic, gastroenterologic, endocrinologic disorders) had higher probability to exhibit COVID-19 symptoms (Figure 3). Lastly, patients who reported to have COVID-19 related symptoms were shown to present with significantly higher pack-years of smoking compared to the ones with no symptoms (P = 0.024) (Figure 4).

As expected, there seems to be a statistically significant relationship between the presence of COVID-19 symptoms and COVID-19 RT-PCR positivity (P < 0.001) (Table 5). Of 109 patients who were tested for COVID-19, 75 (68.8 %) had COVID-19 related symptoms; 30 (40%) cases out of 75 cases with COVID-19 related symptoms, were tested positive for COVID. Thirty-four patients who did not demonstrate any symptoms still gave COVID-19 PCR test, were all tested negative. Of 109 patients who were tested for COVID-19, 43 (39.45 %) had close contact to someone with a confirmed diagnosis of COVID-19; whereas 66 (60.55%) did not have any close contact. Twenty-seven (62.8%) cases out of 43 with close contact to a person diagnosed with COVID-19 had positive RT-PCR result. We found a statistically significant relationship between the history of close contact to someone with a confirmed COVID-19 diagnosis and COVID-19 RT-PCR positivity (P < 0.001) (Table 5). No patient was hospitalized for severe COVID-19 infection.

Binary logistic regression analyses (in which age, gender, BMI, the presence of any other systemic disease and smoking were included as independent variables) were performed
the presence of any other systemic disease were considered as independent variables) were also carried out by taking COVID-19 RT-PCR result (positive or negative) as the dependent variable. As a result, it was found that age, gender, BMI and the presence of at least one systemic illness did not contribute significantly to the outcome of COVID-19 test result.

Taking the presence of COVID-19 symptoms as the dependent variable. Smoking (odds ratio [OR] 2.595; 95% confidence interval: 1.009-6.674; P = 0.048) and the presence of any other systemic illness (OR 6.968; 95% interval: 2.754-17.631; P < 0.001) were associated with an increased risk of developing COVID-19 related symptoms. In addition, logistic regression analyses (in which age, gender, BMI and the presence of any other systemic disease were considered as independent variables) were also carried out by taking COVID-19 RT-PCR result (positive or negative) as the dependent variable. As a result, it was found that age, gender, BMI and the presence of at least one systemic illness did not contribute significantly to the outcome of COVID-19 test result.
females compared to males with a ratio of 3:1 [6,14]. Since patients with HS suffer from acute (bacterial superinfection, lymphadenopathy) and chronic complications of the disease (amyloidosis, chronic disease anemia, lymphedema, lymphatic obstruction, significant scarring, chronic pain, malodor and fistula formation) [15]; early diagnosis and adequate treatment of this debilitating disease are quite essential.

Topical and systemic antibiotics, anti-inflammatory agents, anti-androgens, oral retinoids, immunosuppressive treatments, TNF-α inhibitors (especially adalimumab and infliximab), apremilast, surgical intervention and laser excision repair are among the miscellaneous therapeutic interventions used for HS [16]. Generally, Hurley stage 1 HS is treated

**Table 5. Covid-19 Real-Time PCR results with respect to the presence of Covid-19-related symptoms and close contact to someone with a diagnosis of Covid-19.**

<table>
<thead>
<tr>
<th>Covid-19 Real Time-PCR Results</th>
<th>Covid-19 related symptoms</th>
<th>Close contact to someone with a diagnosis of Covid-19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>Negative</td>
<td>34 (100)</td>
<td>45 (60)</td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0)</td>
<td>30 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>34 (100)</td>
<td>75 (100)</td>
</tr>
</tbody>
</table>

Statistically significant relationships were found between COVID-19 real time-PCR positivity versus history of close contact to someone with a confirmed COVID-19 diagnosis (P < 0.001) and between COVID-19 real time-PCR positivity versus the presence of COVID-19 related symptoms (P < 0.001).

**Conclusions**

HS is one of the most challenging diseases of dermatology, which has a great impact on patients quality of life and presents with various associated comorbidities. The disease is characterized by deep-seated, tender, inflamed, draining nodules and abscesses subsequently leading to sinus tract and scar formation mainly in the flexural areas of the body [11]. HS is most commonly seen in the third and fourth decades of life [12]. Since different clinical entities including furunculosis, nodulocystic acne, epidermoid cyst, cutaneous Crohn disease may be considered in the differential diagnoses of HS, a mean diagnostic delay of 7.2 years has been reported in a study [13]. The disease is more commonly observed in
with topical and systemic antibiotics, surgical procedures; systemic antibiotics, oral retinoids, anti-TNF-α agents, surgical deroofing or laser excision are used for stage 2 and 3 disease [16].

From the start of COVID-19 outbreak in December 2019, the effect of immunosuppressive agents on the clinical course of COVID-19 is gradually being questioned by both physicians and patients [17]. COVID-19 infection is a multiphasic viral disease which commences with an antiviral response phase followed by an hyperinflamatory state [17,18]. The main cytokines that dominate the first (antiviral) phase differ from the cytokines which prevail the hyperinflammatory phase [18]. Interleukin (IL)-15, interferon-α, interferon-β and interferon-γ are the major cytokines responsible for viral clearance whereas TNF-α, IL-17, IL-6 and granulocyte-monocyte colony stimulating factor preponderate during the hyperinflammatory phase [17,18]. Therefore, it seems reasonable to use anti-TNF-α and anti-IL-17 agents during the hyperinflammatory state of COVID-19 since these agents do not seem to affect the course of the antiviral phase [18]. In phase 3 trials of adalimumab for HS, it was shown that there is a slightly escalated risk for total infections and nasopharyngitis by 2.5% but there was no significant difference between adalimumab and placebo group in terms of upper respiratory tract infections [19]. In line with this observation, in our study we found that no statistically significant relationship exists between COVID-19 real-time PCR positivity and the therapeutic interventions used for HS when the treatment modalities are divided into four categories as oral antibiotics ± topical antibiotics, oral retinoids ± topical antibiotics, TNF-α inhibitors ± oral/topical antibiotics and only topical antibiotics (P = 0.657). Also, similar to our study, Marasca et al [20] reported their experience with 93 HS patients during COVID-19 pandemic. In this study, 75 patients were on adalimumab treatment, 15 patients were using oral antibiotics and 3 patients were not on any treatment [20]. Only one patient reported COVID-19 related symptoms which subsided immediately and three patients (one under rifampicin-clindamycin treatment, the two others under adalimumab treatment) had been isolated due to a close contact to someone with a suspected diagnosis of COVID-19, without having positive real-time PCR test result [20]. Furthermore, Molinelli et al [21] declared that none of the 35 patients treated with adalimumab for HS in their cohort group had any symptoms related to COVID-19 and the ongoing biologic treatment was not discontinued in any patient. Supporting the findings of this study, we also did not find any statistically significant difference between the presence of COVID-19 symptoms and the given treatment modalities when categorized as oral antibiotics ± topical antibiotics, oral retinoid, TNF-α inhibitors ± oral/topical antibiotics and topical antibiotics (P = 0.124).

Patients with HS have multiple associated comorbidities including metabolic syndrome, obesity, diabetes mellitus, dyslipidemia, polycystic ovarian syndrome, thyroidal dysfunction, axial spondyloarthritis and cardiovascular-associated adverse events [22]. A recent meta-analysis revealed that cardiovascular diseases, obesity, hypertension, history of smoking, old age are also risk factors for critical and mortal cases of COVID-19 infection [23]. Being male, smoking and being at an age greater than 65 years were shown to be associated with COVID-19 disease progression [23]. Critical COVID-19 cases had higher rates of having underlying diseases such as hypertension, cardiovascular disease and diabetes mellitus compared to the non-critical COVID-19 patients [23]. Even though, in our cohort no patient was needed to be hospitalized for severe COVID-19, we found that the mean age of the patients with positive results of COVID RT-PCR was statistically significantly higher compared to the ones with negative results (P < 0.007). Additionally, patients who demonstrated COVID-19 related symptoms were shown to have statistically significantly higher average age compared to the ones who did not demonstrate any symptoms (P = 0.031). In line with the data in the literature, patients who had any cardiovascular disease (most common one being hypertension) were shown to have COVID-19 related symptoms at a higher rate compared to the ones with no accompanying cardiovascular disease (P = 0.035). Wang et al [24] showed that hypertension prevalence was higher in COVID-19 patients admitted to intensive care unit compared to ones who did not. In our study, we have also showed that patients who had at least one systemic disease had higher proportions of demonstrating COVID-19 symptoms compared to the ones who did not have any known systemic comorbidity. A recent study by Lowe et al [25] revealed that patients with > 30 pack-years of smoking were 2.25 times more likely to be hospitalized. Even though, we did not have any patient who was hospitalized for COVID-19, our study disclosed that patients with COVID-19 symptoms were shown to have statistically significantly higher pack-years of smoking compared to the ones without any symptoms (P = 0.024). Lastly, we found no statistically significant relationship between the presence of COVID-19 symptoms/COVID-19 RT-PCR positivity and gender, BMI, smoking status (current smoker vs non-smoker) and treatment duration (P > 0.05). In contrast, a study which investigated the relationship between COVID-19 and metabolic associated fatty liver disease, showed that obesity significantly increases the risk of having severe COVID-19 disease [26]. Since in our cohort population, not all the patients with COVID-19 related symptoms and with a history of close contact to someone with a confirmed diagnosis of COVID-19, were tested for COVID-19 we might have missed some real positive COVID-19 cases which might have limited our findings.
All in all, we would like underline once again that HS patients have multiple associated comorbidities some of which are also risk factors for critical/mortal COVID-19 disease. In our study, older age, higher pack-years of smoking, having at least one systemic disease, having a cardiovascular disease, were associated with increased risks of having COVID-19 related symptoms whereas higher disease duration of HS and older age were correlated with significantly higher levels of COVID-19 RT-PCR positivity. Treatment type did not seem to contribute significantly to the outcome of COVID-19 RT-PCR test and the incidence of COVID-19 associated symptoms whereas higher disease duration of HS and older age were correlated with significantly higher levels of symptoms. We suggest the ongoing TNF-α inhibitor treatment should be continued in patients with HS, unless a definitive diagnosis of COVID-19 is established.

Our study has some limitations since it was a single center study and no control group was present. Further multicenter, prospective studies with large number of patients are required to support our findings.

References


Evaluation of Sleep Quality in Patients With Genital and Non-Genital Cutaneous Warts: a Prospective Controlled Study

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Key words: warts, sleep quality, Pittsburgh Sleep Quality Index, genital warts


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ABSTRACT

Introduction: Diseases affect sleep quality, and sleep quality may also affect diseases by affecting the immune system. Depending on the immune status of patients with cutaneous warts, the extent of the disease and the response to treatment may vary.

Objectives: This study aimed to characterize the association between cutaneous warts and sleep quality.

Methods: A prospective controlled study was conducted. Patients over 18 years with cutaneous warts were enrolled. The control subjects were healthy, age- and sex-matched people. Demographic and clinical data on the participants were gathered. The sleep quality of participants was evaluated with the Pittsburgh Sleep Quality Index (PSQI).

Results: A total of 138 patients with genital or non-genital cutaneous warts (N = 59, N = 79, respectively) and 83 controls were interviewed. The average global PSQI score of the group with cutaneous warts was significantly higher than that of the control group (1.292 95% confidence interval 1.174-1.422). The rate of poor sleep quality in the patient group was higher than in the control group (odds ratio 3.835). Patients with genital warts had a significantly higher average global PSQI score than patients with non-genital warts (8.61 ± 3.63 versus. 6.98 ± 3.32). Female patients with genital warts had a significantly higher average global PSQI score than male patients with genital warts.

Conclusions: Evaluation of sleep quality in patients with warts, especially in patients with genital warts, may be suggested. The management of sleep disturbances associated with cutaneous warts may help increase the quality of life of patients and may affect disease control.
Introduction

Sleep is an active, restorative, physiological, and neurobiological state that occupies approximately one third of our lives. It is mainly regulated by the homeostatic sleep drive and the circadian system, often called the “central clock,” controlled particularly by the cortisol and melatonin hormones [1,2]. Sleep disruption associated with skin diseases may impair quality of life. Poor sleep quality also has a significant effect on the nervous and immune systems. Moreover, poor sleep quality may induce and/or aggravate skin disease by affecting the regional immune function [3].

Skin also plays a major role in convenient sleep activity by regulating body temperature, peripheral circadian oscillators, ultraviolet (UV)-induced fluctuations in melatonin levels, and cortisol [1]. It has been reported that only one night of sleep deprivation may hinder the recovery of the skin barrier. Natural killer cells and some proinflammatory cytokines (interleukin-1beta/tumor necrosis factor-alfa), which play an important role in the regulation of non-rapid eye movement (NREM) sleep, may increase after sleep disruption [4].

Especially chronic inflammatory skin conditions (eg atopic dermatitis, psoriasis vulgaris, and chronic urticaria) may affect sleep quality [5–7]. Recently, rosacea, lichen planus, hidradenitis suppurativa, acne vulgaris, and Behçet disease have been shown to negatively affect sleep quality [8–12].

Cutaneous warts are a common infectious skin disease caused by human papillomavirus (HPV). Depending on a patient immune status, common warts may appear anywhere on the skin; moreover, spontaneous remission and treatment-resistant lesions may be seen, and it is thought that the immune system is effective in the response to treatment [13]. Although diseases themselves affect the quality of sleep, sleep quality can also affect diseases by affecting the immune system.

Objectives: The aim of this study was to better characterize the association between cutaneous warts and sleep quality.

Methods

Study Participants

A prospective, controlled study was conducted between January and July 2021. The study included patients over 18 years old who were enrolled from tertiary referral dermatology outpatient clinics and diagnosed with cutaneous warts. The control subjects were healthy, age- and sex-matched people.

Exclusion Criteria for Patient Group

Patients aged < 18 years, patients known to have sleep disorders, patients with other chronic and/or any inflammatory systemic and/or dermatologic disorders that may affect sleep quality, and pregnant and lactating women were excluded from the patient group.

Exclusion Criteria for Control Group

Patients aged < 18 years, patients with other chronic and/or any inflammatory systemic and/or dermatologic disorders that may affect sleep quality, and pregnant and lactating women were excluded from the control group.

Ethical Considerations

All participants signed the written consent form before the questionnaire, provided information, and gave permission to use that information in the study regarding the survey. Ethics committee approval was received from the University Scientific Research and Publication Ethics Board.

Survey

In the first section, the demographic and clinical data of the participants were queried. The questions included age, sex, and presence of systemic, autoimmune, and dermatological diseases. The type of warts (genital/non-genital), number of warts (single, 1–5 warts, >5 warts), localization of warts (if non-genital), and duration of the disease were recorded.

The sleep quality of participants was evaluated with the Pittsburgh Sleep Quality Index (PSQI). It is a self-rated questionnaire evaluating sleep quality and sleep disturbances over an interval of the previous month. The questionnaire included 11 questions about subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction. Each domain was scored with 0–3 points. PSQI scores range from 0–21 points. A global PSQI score of 5 or higher reflects poor sleep quality.

Statistical Analysis

SPSS 22.0 package program was used to evaluate the data. The descriptive statistics were the number and percentage for categorical variables and numerical variables as mean, standard deviation, minimum, maximum, and median. The rates in groups were compared using the Chi-squared test, Mann–Whitney U test, and Kruskal–Wallis test. The distribution of variables was measured by the Kolmogorov–Smirnov test. The distribution of variables did not meet the normal distribution condition, the Mann–Whitney U and Kruskal–Wallis tests were used for comparison. Statistical alpha significance level was accepted as P < 0.05.
Results

Demographic and Clinical Characteristics
A total of 138 patients with genital and non-genital cutaneous warts (N = 59, N = 79, respectively) and 83 healthy, sex- and age-matched controls were interviewed. General characteristics of the participants are shown in Table 1. The majority of patients with genital warts were male (89.8%). The sex distribution in patients with non-genital warts was similar. The most frequent localizations of non-genital warts were plantar and palmar (40.5% and 39.2%, respectively).

Comparison of Sleep Quality Between Patient and Control Groups
Patients with cutaneous warts had a significantly higher average global PSQI score than the control group with an odds ratio [OR] of 1.292, 95% confidence interval (CI) 1.174-1.422, with a significantly higher score in all components of the PSQI excluding use of sleeping medication.

Poor sleep quality was observed in 79.7% of the patient group and in 50.6% of the control group (P < 0.05). It was determined that the rate of poor sleep quality in the patient group was higher than in the control group (OR: 3.835; 95% CI: 2.110-6.972) (Table 2).

Table 1. General Characteristics of Participants and Association Between Sleep Quality and Demographic Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Nongenital (N = 79) mean ± SD</th>
<th>Genital (N = 59) mean ± SD</th>
<th>Control (N = 83) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.94±10.23</td>
<td>31.54±10.01</td>
<td>30.20±9.57</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>1.08±1.55</td>
<td>1.20±1.39</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39(49.4)</td>
<td>53(89.8)</td>
<td>47(56.6)</td>
</tr>
<tr>
<td>Female</td>
<td>40(50.6)</td>
<td>6(10.2)</td>
<td>36(43.4)</td>
</tr>
<tr>
<td>Number of warts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>36(45.6)</td>
<td>1(1.7)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>28(35.4)</td>
<td>16(27.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>15(19.0)</td>
<td>42(71.2)</td>
<td></td>
</tr>
<tr>
<td>Localization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>31(39.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plantar</td>
<td>32(40.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial</td>
<td>9(11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmoplantar</td>
<td>4(5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3(3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-genital (N = 79)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30 years</td>
<td>56</td>
<td>33</td>
<td>8.33±3.72</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>23</td>
<td>26</td>
<td>8.96±3.56</td>
</tr>
<tr>
<td>z/P</td>
<td>-0.786/0.432</td>
<td>-0.797/0.425</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>53</td>
<td>8.30±3.65</td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>6</td>
<td>11.33±2.06</td>
</tr>
<tr>
<td>z/P</td>
<td>-0.015/0.988</td>
<td>-2.102/0.036*</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 year</td>
<td>65</td>
<td>42</td>
<td>8.66±3.88</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>14</td>
<td>17</td>
<td>8.47±3.04</td>
</tr>
<tr>
<td>z/P</td>
<td>-0.574/0.566</td>
<td>-0.109/0.913</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation; z = Mann Whitney U test.
* P < 0.05.
warts (11.33 ± 2.06 versus 8.30 ± 3.65). There was no significant difference in sleep quality regarding age, number of warts, or disease duration (Table 1).

Conclusions

Although the reason cannot be fully clarified, chronic inflammatory skin diseases (eg atopic dermatitis, psoriasis vulgaris, chronic urticaria) and rosacea, lichen planus, hidradenitis suppurativa, acne vulgaris and Behçet disease are shown to have a negative effect on sleep quality [5–12]. Apart from symptoms such as pain and itching caused by diseases, the

### Table 2. Comparison of Sleep Quality Between Patient and Control Group.

<table>
<thead>
<tr>
<th>Pittsburgh Sleep Quality Index (PSQI) and PSQI domains</th>
<th>Patients (N = 138) mean ± SD</th>
<th>Control (N = 83) mean ± SD</th>
<th>z/P</th>
<th>Odds Ratio a (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global PSQI</td>
<td>7.68 ± 3.53</td>
<td>4.92 ± 2.91</td>
<td>-5.549/0.000*</td>
<td>1.292 (1.174-1.422)</td>
</tr>
<tr>
<td>Subjective sleep quality</td>
<td>1.42 ± 0.64</td>
<td>1.18 ± 0.68</td>
<td>-2.498/0.012*</td>
<td>1.764 (1.152-2.701)</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>1.55 ± 0.88</td>
<td>1.03 ± 0.86</td>
<td>-4.127/0.000*</td>
<td>1.955 (1.405-2.720)</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>1.18 ± 1.06</td>
<td>0.77 ± 0.83</td>
<td>-2.738/0.006*</td>
<td>1.541 (1.153-2.060)</td>
</tr>
<tr>
<td>Habitual sleep efficiency</td>
<td>0.55 ± 0.74</td>
<td>0.12 ± 0.32</td>
<td>-4.813/0.000*</td>
<td>4.587 (2.299-9.154)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1.23 ± 0.63</td>
<td>0.74 ± 0.55</td>
<td>-5.460/0.000*</td>
<td>3.936 (2.316-6.690)</td>
</tr>
<tr>
<td>Use of sleeping medication</td>
<td>0.47 ± 0.91</td>
<td>0.27 ± 0.70</td>
<td>-1.648/0.099</td>
<td>1.363 (0.952-1.950)</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>1.25 ± 1.01</td>
<td>0.79 ± 0.77</td>
<td>-3.210/0.001*</td>
<td>1.704 (1.251-2.321)</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>N (%)</td>
<td>N (%)</td>
<td>x²/P</td>
<td></td>
</tr>
<tr>
<td>Poor sleep quality</td>
<td>110 (79.7)</td>
<td>42 (50.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good sleep quality</td>
<td>28 (20.3)</td>
<td>41 (49.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\* SD = standard deviation; z = Mann Whitney U test; x² = Xi square test.
\* P < 0.05; a Logistic regression analysis.

### Table 3. Comparison of Sleep Quality Between Patients With Genital and Non-genital Warts.

<table>
<thead>
<tr>
<th>Pittsburgh Sleep Quality Index (PSQI) and PSQI domains</th>
<th>Non-genital (a) (N = 79) mean ± SD</th>
<th>Genital (b) (N = 59) mean ± SD</th>
<th>Control (c) (N = 83) mean ± SD</th>
<th>KW/p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global PSQI</td>
<td>6.98 ± 3.32</td>
<td>8.61 ± 3.63</td>
<td>4.92 ± 2.91</td>
<td>36.790/0.000*</td>
</tr>
<tr>
<td>Subjective sleep quality</td>
<td>1.39 ± 0.70</td>
<td>1.47 ± 0.56</td>
<td>1.18 ± 0.68</td>
<td>6.904/0.032*</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>1.46 ± 0.85</td>
<td>1.66 ± 0.90</td>
<td>1.03 ± 0.86</td>
<td>18.222/0.000*</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>1.06 ± 1.01</td>
<td>1.33 ± 1.10</td>
<td>0.77 ± 0.83</td>
<td>9.666/0.008*</td>
</tr>
<tr>
<td>Habitual sleep efficiency</td>
<td>0.54 ± 0.81</td>
<td>0.55 ± 0.65</td>
<td>0.12 ± 0.32</td>
<td>23.997/0.000*</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1.13 ± 0.61</td>
<td>1.37 ± 0.64</td>
<td>0.74 ± 0.55</td>
<td>33.497/0.000*</td>
</tr>
<tr>
<td>Use of sleeping medication</td>
<td>0.36 ± 0.78</td>
<td>0.62 ± 1.04</td>
<td>0.27 ± 0.70</td>
<td>4.411/0.110</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>1.01 ± 0.98</td>
<td>1.57 ± 0.98</td>
<td>0.79 ± 0.77</td>
<td>21.785/0.000*</td>
</tr>
</tbody>
</table>

KW = Kruskal Wallis test.
\* P < 0.05; a Bonferroni’s correction: P < 0.0167.

**Comparison of Sleep Quality Between Patients With Genital and Non-genital Warts**

Patients with genital warts had a significantly higher average global PSQI score than patients without genital warts (8.61 ± 3.63 versus 6.98 ± 3.32), with a significantly higher score in 2 components of the PSQI, ie sleep disturbance and daytime dysfunction (Table 3; Figure 1).

**Association Between Sleep Quality and Demographic Characteristics**

Female patients with genital warts had a significantly higher average global PSQI score than male patients with genital warts (11.33 ± 2.06 versus 8.30 ± 3.65). There was no significant difference in sleep quality regarding age, number of warts, or disease duration (Table 1).

**Conclusions**

Although the reason cannot be fully clarified, chronic inflammatory skin diseases (eg atopic dermatitis, psoriasis vulgaris, chronic urticaria) and rosacea, lichen planus, hidradenitis suppurativa, acne vulgaris and Behçet disease are shown to have a negative effect on sleep quality [5–12]. Apart from symptoms such as pain and itching caused by diseases, the
psychosocial effects of dermatological diseases cannot be denied. Sleep quality is also one of the most important of these psychosocial effects. For this reason, the effects of dermatological diseases on sleep quality have been frequently investigated in recent studies.

In fact, although diseases themselves affect sleep quality, sleep quality may also affect diseases by affecting the immune system. Sleep disorders may result in some changes in immune system functions. In accordance with the association between cytokines, host immune function, and the sleep-wake cycle, sleep disturbance may play a role in the inflammatory cascade that can result in a chronic inflammatory state [1].

Cutaneous warts are a common disease, and depending on the immune status of the person, the extent of the disease and the response to treatment may vary [14]. In the literature, only one study has mentioned the effect of cutaneous warts on sleep quality [15]. In the study of Liu et al,
in which 215 patients with palmar/plantar warts were evaluated. 11.0% of the patients reported poor sleep quality; however, this study was conducted without questionnaires or a control group. Although the reason is not mentioned, it was observed that the treatment response was low in those with poor sleep quality [15]. Our study is significant in that it is the first controlled study in this respect and that patients with genital warts (ie as opposed to only non-genital warts) were also evaluated.

In our study, patients with cutaneous warts had a significantly higher average global PSQI score than that of the control group. Here, the disease itself, treatment processes, and response or non-response to treatment may affect sleep quality. However, the sleep quality of the patients may also affect their immune status, thus affecting the elimination of the virus or the extent of the virus and the response to treatment. Sleep is actually an immunological activity. Human sleep consists of two phases: REM (rapid eye movement) and NREM (non-REM) sleep. Natural killer cells and some proinflammatory cytokines (interleukin-1beta/tumor necrosis factor-alfa), which play an important role in the regulation of NREM sleep, may increase after sleep disruption [4]. However, slow-wave sleep (deep sleep) plays a role in reducing immune system activation, while sleep deprivation can activate the immune system, leading to an increase in IL-1, IL-6, TNF a, leukocytes, NK, and monocyte cells. Hypothalamic-pituitary-adrenal (HPA) activation reduces the sleep-enhancing effects of cytokines, decreases non-REM sleep, and increases wakefulness in the advanced stages of inflammation [16].

Patients with genital warts had a significantly higher average global PSQI score than patients with non-genital warts and controls in this study. The transmission of genital warts by sexual contact and the feeling of guilt and shame caused by it, relapses during treatment, and the risk of malignancy are the most important causes of psychological damage in patients. In addition, the sexual life of patients may be affected [17]. The degree of this impact on quality of life may also affect sleep quality.

Female patients with genital warts showed a significantly higher average global PSQI score than male patients with genital warts in this study. Evaluating the literature, it has been shown that the sleep quality of women might be more affected.

The shortcoming of the study is that concurrent quality of life was not evaluated. In addition, since the treatment options were not standard in all patients, it was not evaluated whether the sleep quality of the patients had an effect on the response to treatment.

Our study reveals the association between poor sleep and cutaneous warts. Cutaneous warts seem to have an effect on sleep, but perhaps the reverse direction is also true. Evaluation of sleep quality in patients with warts, especially in patients with genital warts, may be suggested. The management of sleep disturbances in cutaneous warts may help increase the quality of life of patients and may affect disease control.

References


The Hunt for Baby Melanomas: A Prospective Study of the Dermoscopy Features on 100 Small Melanoma Cases with in Vivo Surface Diameters up to a Maximum of 6 mm

John H Pyne1, Sarah MacDonald1, Susan M Beale1, Esther Myint1, Wei W Huang1, Simon Paul Clark1, Andrew Trang1

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Key words: early small melanoma, dermoscopy, confocal microscopy, pigmented hair follicles, pseudopods

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ABSTRACT

Introduction: Early diagnosis can improve melanoma prognosis. Dermoscopy can enhance early melanoma recognition.

Objectives: Examine the dermoscopy features of early melanoma up to a maximum surface diameter of 6 mm.

Methods: Consecutive melanoma cases were collected from two medical practices in Sydney, Australia 2019-2021. Dermoscopy features were recorded for melanomas by maximum surface diameter, to the nearest 0.1 mm, to a limit of 6 mm.

Results: Total cases numbered 100; with males (N = 48) and females (N = 52), melanoma in situ (MIS, N = 96) and invasive (N = 4). The most frequent anatomic sites on both males and females were back (males N = 20, females N = 16) then knee or leg (males N = 8, females N = 12). Minimum respective MIS diameters for males/females was 1.2/2.0 mm and for invasive cases 2.0/3.4 mm. Highest frequency dermoscopy features were: light brown, dark brown, gray and asymmetric melanoma shape. Brown pigment in hair follicles were more frequent on legs compared to other anatomic sites (odds ratio [OR] 14.6; 95% CI 1.29-165.17, P 0.03). Pseudopods were substantially increased in frequency comparing diameters less than 4 mm with 4 up to 6 mm (OR 8.81; 95% CI 1.05-73.9, P 0.004). Structureless area cases recorded increased gray (OR 7.08; 95% CI 1.61-31.11, P=0.01).
or greater were excluded. Cases with known previous topical or ablative therapies, any previous partial biopsy or adjacent scars were also excluded. Each case was an attempted full excision with a 2mm dermoscopy identified margin. A dermoscopy image for each case was submitted along with each tissue specimen to the reporting pathologists. Further, representative Vivascope 1500 confocal images were also available to the reporting pathologists for difficult to diagnose cases.

Excised tissue was examined routinely with hematoxylin and eosin staining followed with SOX 10 and PRAME stains if required. Inclusion of each case required an independent histopathological diagnosis of melanoma from each of two experienced dermato-histopathologists. Cases where only one of two dermato-histopathologists reported melanoma were also excluded.

Atypical vessels were defined as dermoscopy identified vessels within the melanoma “footprint” displaying a different morphology or increased number of vessels per unit area compared to vessels in the adjacent background skin out to 10 mm from the edge of the melanoma, an example is displayed in Figure 5B. Asymmetric shape relates to the silhouette of the melanoma. Atypical network was defined when the width of lines forming a reticular brown network exceeded the diameter of the adjacent dermal papillae, see Figure 5C. Polygons were angular lines in polygonal shapes [8], see Figure 6B. Structureless areas displayed no distinct features within the area concerned and had to occupy at least 20% of the melanoma “footprint”, see Figure 5A.

Results
All cases presented as macules with no overt surface elevation. Patients had predominately northern European ancestry with fair skin and were typically Australian born. Following histopathologic diagnostic confirmation, a total of 100 melanoma cases were collected. Cases on males numbered 48 (mean age 56) and on females 52 (mean age also 56), see Table 1. Study cases by anatomic site and sex are set out in Table 2. No cases were recorded on the following sites on either sex: scalp, eyelid, chin, cutaneous or mucosal lip, hand, fingers or toes. Females had an increased frequency of

Introduction
Primary cutaneous melanoma prognosis is optimal when early diagnosis leads to prompt effective intervention. However, small diameter early melanoma cases are often feature poor and may be difficult to recognize. The use of dermoscopy has been shown to enhance diagnostic accuracy for melanoma [1-3]. Some recent publications have addressed the dermoscopy features of small early melanoma [4,5]. Additional evidence collated with the dermoscopy features of smaller melanomas may facilitate diagnosing these early cases [6].

Recent commentary has questioned the value of diagnosing melanoma with small diameters and suggested suspicious pigmented lesions not be biopsied if less than 6mm diameter [7].

Objectives
The main purpose of this study was to quantify the dermoscopy features of melanoma cases with an in vivo maximum horizontal diameter of up to and including 6 mm. A second aim was to record how these dermoscopy features varied by the surface diameters in 1mm increments for melanomas presenting with a surface diameter of 6 mm or less.

Methods
Consecutive melanoma cases were prospectively collected from routine workflow in 2 medical practices in Sydney, Australia over 28 months from 2019 until 2021. One practice was a referral practice with Vivascope 1500 confocal capability. The second practice was a primary care designated skin cancer clinic. Ethics Approval was provided by the University of Queensland, Brisbane Australia (2016001221). All patients in the study provided informed consent for their data to enter the study. There were no exclusions based on patient age or anatomic site.

Dermoscopy using either a Heine IC1 or VivaCam dermatoscope recorded each case in vivo maximum horizontal diameter, measured in 0.1 mm increments, up to and including 6.0 mm. Cases with a maximum surface diameter 6.1mm or greater were excluded. Cases with known previous topical or ablative therapies, any previous partial biopsy or adjacent scars were also excluded. Each case was an attempted full excision with a 2mm dermoscopy identified margin. A dermoscopy image for each case was submitted along with each tissue specimen to the reporting pathologists. Further, representative Vivascope 1500 confocal images were also available to the reporting pathologists for difficult to diagnose cases.

Excised tissue was examined routinely with hematoxylin and eosin staining followed with SOX 10 and PRAME stains if required. Inclusion of each case required an independent histopathological diagnosis of melanoma from each of two experienced dermato-histopathologists. Cases where only one of two dermato-histopathologists reported melanoma were also excluded.

Atypical vessels were defined as dermoscopy identified vessels within the melanoma “footprint” displaying a different morphology or increased number of vessels per unit area compared to vessels in the adjacent background skin out to 10 mm from the edge of the melanoma, an example is displayed in Figure 5B. Asymmetric shape relates to the silhouette of the melanoma. Atypical network was defined when the width of lines forming a reticular brown network exceeded the diameter of the adjacent dermal papillae, see Figure 5C. Polygons were angular lines in polygonal shapes [8], see Figure 6B. Structureless areas displayed no distinct features within the area concerned and had to occupy at least 20% of the melanoma “footprint”, see Figure 5A.

Melanomas with edge angulation were noted in 20%-50% of cases across diameters 1-6 mm, less frequent were pigmented circles and polygons.

Conclusions: Watch out! MIS presented with a surface diameter of just 1.2 mm and invasive melanoma 2.5 mm. Pseudopods were a strong clue to melanomas with a surface diameter less than 5mm. We found melanomas on leg sites displayed more frequent pigmented hair follicles.
Table 1. Patient characteristics by sex and in vivo melanoma surface diameter.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male (N = 48)</th>
<th>Female (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (min, max)</td>
<td>18-78</td>
<td>29-90</td>
</tr>
<tr>
<td>Mean</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>IQR</td>
<td>45-66</td>
<td>42-69</td>
</tr>
<tr>
<td>Diameter of lesion (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>3.1-4.0</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>4.1-5.0</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>5.1-6.0</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

IQR = interquartile range.

Table 2. Number of melanoma cases by sex and anatomic site.

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Male (N = 48)</th>
<th>Female (N = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Forehead</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nose</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neck</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chest</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Back</td>
<td>20 (1 invasive 0.5 mm)</td>
<td>16</td>
</tr>
<tr>
<td>Upper arm</td>
<td>2</td>
<td>8 (1 invasive 0.4 mm)</td>
</tr>
<tr>
<td>Forearm</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2 (1 invasive 0.5 mm)</td>
<td>0</td>
</tr>
<tr>
<td>Thigh</td>
<td>2 (1 invasive 0.4 mm)</td>
<td>3</td>
</tr>
<tr>
<td>Knee or leg</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Foot</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of melanoma cases by sex and anatomic site. All cases were melanoma in situ except four invasive cases. These 4 invasive cases are identified by site and respective Breslow invasion depth.

Melanomas on the upper arm compared to males: odds ratio [OR] 4.16, 95% CI 0.836-20.7, P 0.08. For knee combined with leg sites females also had more melanomas compared to males: OR 1.49, 95% CI 0.545-4.05, P 0.44. Males recorded more melanomas on the back compared to females: OR 1.61, 95% CI 0.707-3.67, P 0.26. However, none of these anatomic site differences reached statistical significance.

Melanoma in situ was reported in 96 cases. The average surface diameter for the melanoma in situ cases was 3.9 mm (N = 96) and for the invasive melanoma cases 3.6 mm (N = 4). On males the smallest recorded surface diameter for a melanoma in situ case was 1.2 mm (chest) and for invasive cases 2.5 mm (back). In comparison, on females the smallest diameter melanoma in situ case was 2.0 mm (thigh) and the single invasive case 3.4 mm (upper arm). Three invasive melanoma cases were recorded on males: one with a Breslow of 0.4 mm (thigh) and the other two cases both had a Breslow of 0.5 mm (abdomen and back), again see Table 2. Only one male case recorded a mitotic count: 1 per mm² from the case on the back. The only invasive melanoma on a female was on the upper arm with a Breslow of 0.4 mm and 0 mitotic count. There was no microscopic evidence of tumor induced ulceration on all four invasive cases. No cases of acral, nodular or desmoplastic melanoma were recorded in this study.

When using dermoscopy the colors identified within the melanoma with the highest percentage presence in descending order were: light brown, dark brown and gray, see Figure 1. Figure 1 also displays these dermoscopy features with a typical frequency range from 30% up to 100% across the recorded range of diameters. In comparison, other dermoscopy identified features with moderate prevalence (frequency of feature from 15% up to 50%) are set out in Figure 2. Lower prevalence features (frequency at or below 25% of cases) are displayed in Figure 4. Although low in frequency, typically less than 10% of cases, polygons were recorded in cases over 2 mm diameter.
All colors identified (light and dark brown, gray and pink) within the melanoma rose in frequency as the diameters increased from 1 to 6 mm, again see Figure 1. The exception to this rise in frequency of color was black which had frequencies 20% to 40% over the full range of diameters, see Figure 2. Other dermoscopy features also increased in frequency as diameters increased: asymmetric melanoma shape (30 to 65%), atypical network (20 to 57%), grey circles (0 to 25%) and polygons (0 to 12%). Atypical vessels fell from 20 to zero then increased to 12%. Angles at the edge of the melanoma increased then decreased with an overall range of frequencies from 20% to 47%.

A striking finding in this study was how focal pseudopods (11% of all cases, N = 11/100) can facilitate very small diameter melanoma recognition, see Figure 3. When comparing smaller melanomas with a surface diameter less than 4.0 mm to larger diameter 4.0 to 6.0 mm inclusive cases the presence of pseudopods was substantially increased (OR 8.81, 95% CI 1.03-73.9, P 0.004). Brown pigment within hair follicle infundibula were recorded in a total of eight cases (8%, 8/100). On the leg (3 out of these 8 cases) pigment in follicles were more frequent compared to other sites (OR 14.6, 95% CI 1.29-165.17, P 0.03). Pink occurred more frequently on non-leg sites (N = 40) out of all other sites combined (N = 43), OR 4.72, 95% CI 1.22-18.2, P 0.02. Finally, structureless areas were associated with an increased presence of gray within the whole melanoma “footprint” (OR 7.08, 95% CI 1.61-31.11, P 0.01).

Conclusions

Nearly all cases in this study were detected by pattern analysis involving attention to features dominated by melanin pigment. Predominant color pink with scant minimum pigment was observed in only one case. There were no cases displaying all pink without brown. There may be a selection bias favoring brown pigment cases. Amelanotic melanoma cases: those without clinical or dermoscopy evidence of brown pigment, may be underrepresented.

We integrated and combined all the relevant clinical, dermoscopy and confocal features to facilitate diagnosis as previously described to minimize the risk of missing a melanoma [9]. In equivocal cases all relevant information was readily available to the reporting histopathologists. This may have increased our diagnostic “pick up” rate compared to other studies.

We found very similar mean surface diameters for melanoma in situ (3.9 mm) and invasive melanoma (3.6 mm). Previous studies have reported melanoma in situ and invasive melanomas with diameters up to and including 3 mm [10],

![Figure 1. Dermoscopy features with high prevalence by in vivo melanoma surface diameter.](image-url)
Figure 2. Dermoscopy features with moderate prevalence by in vivo melanoma surface diameter.

Figure 3. Dermoscopy features with progressive variation in prevalence by in vivo melanoma surface diameter.
Figure 4. Dermoscopy features of melanoma with low prevalence over all surface diameters.

Figure 5. (ABC) Displaying pseudopods, structureless area, atypical vessels, atypical network and angular edge of melanoma.
later in development rather than originating or appearing up out of infundibula in earlier stage development.

Our finding increased grey associated with structureless areas in the melanoma may indicate increased melanin at the level of the papillary dermis following a host immune response. This finding could be substantiated with further investigation. Atypical vessels noted in this study were typically an increase in dot vessels per unit area within the melanoma. These dot vessels may represent increased perfusion in the superficial dermal vessels as previously described [12] rather than true tumor induced neovascularization.

Clinicians and pathologists need to be vigilant with small suspicious cases displaying melanoma associated features presenting with diameters much less than 6 mm. We found the lowest recognition threshold diameter for melanoma in situ was 1.2 mm and for invasive melanomas 2.5 mm.

In descending order, we found the following colors present in melanomas with a maximum surface diameter up to 6 mm: light brown, dark brown, grey, pink then black. Other dermoscopy features which were clues to these small early melanomas include: asymmetric macule shape, angulation on the edge of the melanoma, pseudopods, pigmented follicular infundibula, structureless areas, atypical network and pigmented circles.

These findings sound a warning to both clinicians and pathologists that macules with an in vivo diameter of 6 mm or even substantially less require vigilance for melanoma diagnosis and even early metastatic potential. Only 5 of our cases had a maximum surface diameter less than 2 mm. Except for the presence of pseudopods the lack of distinctive features in these very small cases may account for such a low detection rate.

A dermoscopy image of each case was submitted to the reporting Pathologists at the same time as the tissue submission. Confocal microscopy images were also available to enhance diagnostic certainty for some cases as this has been demonstrated [11]. Future investigation could quantify the contribution of this additional information in small size cases compared to just examining the histology slides and the routine notes supplied by the clinician on the pathology request documentation.

One explanation of brown pigment within a hair follicle infundibulum is melanocytes producing melanin at this site. We found melanomas in our study with a diameter three mm or less did not display brown pigment in hair follicle infundibula. Pigment was found in larger melanomas with diameters over 3 mm, see Figure 3. This finding suggests melanin producing melanocytes spread down into the infundibula later in development rather than originating or appearing up out of infundibula in earlier stage development.

Our finding increased grey associated with structureless areas in the melanoma may indicate increased melanin at the level of the papillary dermis following a host immune response. This finding could be substantiated with further investigation. Atypical vessels noted in this study were typically an increase in dot vessels per unit area within the melanoma. These dot vessels may represent increased perfusion in the superficial dermal vessels as previously described [12] rather than true tumor induced neovascularization.

Clinicians and pathologists need to be vigilant with small suspicious cases displaying melanoma associated features presenting with diameters much less than 6 mm. We found the lowest recognition threshold diameter for melanoma in situ was 1.2 mm and for invasive melanomas 2.5 mm.

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References


Reflectance Confocal Microscopy Follow-up of Multifocal Superficial Basal Cell Carcinomas Treated With Imiquimod 5% Cream

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Key words: superficial basal cell carcinoma, imiquimod 5% cream, reflectance confocal microscopy, multifocal

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ABSTRACT

Introduction: Patients with multifocal superficial basal cell carcinomas (sBCC) require a non-invasive treatment and follow-up with a non-invasive technique. Imiquimod 5% cream is a new non-invasive therapy for BCC. Reflectance confocal microscopy (RCM) is a non-invasive, real-time imaging technique.

Objectives: To evaluate and describe the feasibility and efficacy of imiquimod 5% cream for the treatment of multifocal sBCC using RCM.

Methods: The efficacy of imiquimod 5% cream for the treatment of multifocal sBCC was evaluated, as well as the potential of RCM for assessing therapeutic effects. We reported four patients with 34 sBCC lesions were treated with imiquimod 5% cream. RCM was performed in the baseline and at 12 weeks, 24 weeks and 52 weeks after starting treatment.

Results: Of 34 lesions treated with imiquimod 5%, 32 responded to the treatment and showed complete clinical clearing. Two subclinical BCC lesions were identified by RCM. The complete tumor clearance rate was 88.2%, and the efficiency rate was 97.1%. No lesion recurred at 24-month follow-up. RCM identified previously described confocal features of BCC and was more sensitive than clinical examination. Local skin reactions were relieved after expectant treatment.

Conclusions: Imiquimod 5% cream may be useful for the treatment of multifocal sBCC, and its side effects are easy to manage. RCM can be used for non-invasive monitoring of treatment response and improved the tumor clearance rate.
Introduction

Basal cell carcinoma (BCC) is the most common skin cancer worldwide. Although surgical treatment of BCC is the gold standard, patients may be reluctant to accept invasive treatment by reason of multifocal BCC-lesions. In recent years, non-invasive therapies have been widely used for the treatment of superficial (s)BCC [1,2]. Imiquimod is a new local treatment that can remove tumor tissues without injuring the surrounding normal tissues. However, histological evidence of tumor clearance is difficult to obtain. In vivo reflectance confocal microscopy (RCM) is a non-invasive, real-time imaging technique that provides near histologic level resolution cross-sectional images of superficial layers of the skin. RCM can be used to diagnose and monitor treatment effectiveness in BCC [3-5].

Objectives

The aim of this study was to evaluate and describe the feasibility and efficacy of imiquimod 5% cream for the treatment of multifocal sBCC using RCM.

Methods

Four patients (3 females and 1 male) with diagnoses of sBCC, with 2 or more lesions, and aged from 27 to 76 years (mean 56 years) were included in the study.

The patients presented with 34 sBCC appearing as mild reddish-brown patches and pigmented patches (Figure 1A). The patients were overall healthy and had no other symptoms associated with Gorlin Syndrome. All lesions were diagnosed clinically, and BCC features were confirmed under RCM. All the lesions were confirmed as superficial (s)BCC histologically (Figure 1B). Each lesion was treated with 5% imiquimod cream (Aldara®; 3M Pharmaceuticals).

Imiquimod 5% cream was applied once daily for 5 days/week for 12 weeks. Treatment visit was performed once every two weeks. Treatment ended when there was no clinical or RCM evidence. If there is no response or insufficient response, treatment was continued and reevaluated every 2 weeks, until complete clinical response was obtained. The imiquimod cream was applied before going to bed and removed with soap and water approximately 8 hours later. The treatment area was not covered except in cases of bleeding or excessive discharge from the wound. Each treatment field encompassed the lesion and 1.0 cm margins surrounding the visible BCC lesion.

Each lesion was followed up by RCM (Vivascope 1500, Lucid Technologies) at 12 weeks, 24 weeks and 52 weeks after the start of imiquimod treatment. Baseline and follow-up images were collected. The RCM images were evaluated by two experienced physicians. If there was discordance between the two evaluators, a consistent interpretation was obtained from a third reviewed. Therapeutic effects were determined by tumor size combined with RCM imaging features.

Results

A total of 34 BCC lesions were included in the analysis. The tumor size ranged from 0.5 to 3 cm in the maximum diameter (mean, 1.4 cm). Lesions were located in the neck area (N = 3), scalp (N = 2), chest (N = 8), abdomen (N = 5), back (N = 5), lower extremities (N = 6), and upper extremities (N = 5). The durations of the drug application period varied from 8 weeks to 28 weeks, with an average of 18.6 ± 6.9 weeks.

![Figure 1.](image-url) (A) Multifocal BCCs in the chest area before treatment. (B) Histopathology showed the basaloid cords and basaloid island connected to the epidermis (H&E, magnification 40×).
Reflectance Confocal Microscopy Analysis

RCM imaging details are provided in Table 1. RCM criteria previously described were used for the diagnosis of BCC [6-8]. The RCM criteria for the diagnosis of BCC include principal criteria (≥2 principal criteria present): tumor islands, elongated and polarized nuclei, peripheral palisading; and secondary criterion (≥3 secondary criterion present): keratinocyte atypia, cords connected to the epidermis, bright particles, peri-tumoral clefting, increased vascularization, and dendritic cells inside tumor islands (Figure 2). At the 12-week, 24-week and 52-week follow-up evaluations, there was no RCM evidence in 22 lesions, 26 lesions, and 30 lesions, respectively (Figure 3). At the 52-week follow-up, residual BCC was detected by RCM in 4 of 34 sites (11.8%), and there was no clinical manifestation in two lesions. The area of three lesions was obviously reduced, but no effect was observed in one lesion. The complete tumor clearance rate was 88.2%, and the efficiency rate was 97.1%. In the residual lesion, treatment with imiquimod 5% cream was discontinued, and surgical treatment was performed. No lesion recurred at 24-month follow-up.

Local Skin Reactions

The patient is still under clinical and RCM monitoring. All lesions had good cosmetic outcomes except hypopigmentation in eight lesions (23.5%). Local skin reactions (LSR)

Table 1. Reflectance confocal microscopy characteristics of basal cell carcinomas before (baseline) treatment with imiquimod and at 12, 24 and 52 weeks after treatment.

<table>
<thead>
<tr>
<th>Reflectance confocal microscopy</th>
<th>Baseline, % (No.)</th>
<th>12-week follow-up, % (No.)</th>
<th>24-week follow-up, % (No.)</th>
<th>52-week follow-up, % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor islands</td>
<td>82.4 (28)</td>
<td>23.5 (8)</td>
<td>17.6 (6)</td>
<td>2.9 (1)</td>
</tr>
<tr>
<td>Elongated and polarized nuclei</td>
<td>79.4 (27)</td>
<td>23.5 (8)</td>
<td>14.7 (5)</td>
<td>2.9 (1)</td>
</tr>
<tr>
<td>Peripheral palisading</td>
<td>52.9 (18)</td>
<td>20.6 (7)</td>
<td>8.8 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Keratinocyte atypia</td>
<td>100 (34)</td>
<td>35.3 (12)</td>
<td>23.5 (8)</td>
<td>11.8 (4)</td>
</tr>
<tr>
<td>Peri-tumoral clefting</td>
<td>17.6 (6)</td>
<td>5.9 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dendritic cells inside tumor islands</td>
<td>97.1 (33)</td>
<td>35.3 (12)</td>
<td>20.6 (7)</td>
<td>8.8 (3)</td>
</tr>
<tr>
<td>Cords connected to the epidermis</td>
<td>94.1 (32)</td>
<td>32.4 (11)</td>
<td>17.7 (6)</td>
<td>5.9 (2)</td>
</tr>
<tr>
<td>Increased vascularization</td>
<td>82.4 (28)</td>
<td>26.5 (9)</td>
<td>5.9 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bright particles</td>
<td>70.6 (24)</td>
<td>35.3 (12)</td>
<td>23.5 (8)</td>
<td>5.9 (2)</td>
</tr>
</tbody>
</table>

Figure 2. Reflectance confocal microscopy (RCM) image of basal cell carcinoma (BCC). (A) Keratinocyte atypia (blue arrowheads). (B) Increased vascularization (blue arrowheads). (C) Peri-tumoral clefting (blue arrowheads). (D) Tumor islands (blue arrowheads) and bright particles (red arrowheads). (E) Elongated and polarized nuclei (red arrowheads). (F) Dendritic cells inside tumor islands (blue arrowheads). (G) Cords connected to the epidermis (blue arrowheads). (H) Peripheral palisading (blue arrowheads).
including erythema, edema, dryness, crusting, and erosion were present in nine lesions (26.5%). They were relieved after expectant treatment with moisturizer. Treatment was interrupted for 1 week or 2 weeks for recovery in serious cases.

Conclusions

RCM provides a useful, noninvasive tool for the diagnosis of BCC. The presence of two or more RCM criteria is 100% sensitive for the diagnosis of BCC, and with 4 or more RCM criteria present the specificity was 95.7% [9]. In this study, 5 criteria or more present could be diagnosed as BCC, by which diagnostic coincidence rate was 100% comparing with pathological outcome. Our study confirmed that imiquimod 5% cream is highly effective for the treatment of multifocal sBCC. Notably, RCM features were not present after treatment with imiquimod 5% cream in 30 of 34 lesions. Before treatment, the RCM criteria for the diagnosis of BCC were detected as described in Table 1. At 12 weeks after treatment, these RCM parameters were reduced by approximately 64.7% of the initial values. At the 52-week follow-up, clinical evaluation showed that 94.1% (32 of 34 lesions) achieved complete clearance, whereas RCM showed that 88.2% (30 of 34 lesions) of lesions had lost BCC features. Residual BCC was identified upon RCM examination in two lesions that did not present clinical manifestation. RCM improved the tumor clearance rate during follow-up. The presence of increased dendritic structures and bright particles in the epidermis (Figure 3F) after 12 weeks of imiquimod application indicate that imiquimod 5% has initiated an immune response and is a reliable biomarker for predicting treatment response.

Surgery is the gold standard for treatment of BCC. However, in some cases such as elderly patients who are too frail to withstand excisional surgery, or patients with multifocal BCC-lesions, non-invasive therapies are needed. Studies evaluating BCCs of the trunk or extremities suggest that imiquimod is as effective as surgical treatment regarding clinical cure rates and it achieves good to excellent cosmetic outcomes [10-11]. In this study, we also confirmed that imiquimod 5% is effective for the treatment of multiple sBCCs. The complete tumor clearance rate was 88.2%, higher than those of documents reported [1,2,12], which may be credited to RCM surveillance. The therapeutic regimens were different in the previous studies [12-15]. Consistent with previous studies [16-17], the imiquimod dosing regimen of 5 times per week for 12 weeks is an effective treatment for sBCC.

In this study, the most common side effects were erythema and hypopigmentation, and recovery was gradual. The erythema may be a sign of an immune response in the epidermis. LSRs mainly occurred during the first 3 months of therapy.

The present study had some limitations. This was an open study with no control group and it included only four patients. Larger clinical studies with longer follow-up periods are necessary. In conclusion, we confirmed the efficacy
of imiquimod 5% for the treatment of multiple sBCC and showed that RCM is a valuable tool for non-invasive monitoring of treatment response.

References


Various Application of Tofacitinib and Ruxolitinib (Janus Kinase Inhibitors) in Dermatology and Rheumatology: A Review of Current Evidence and Future Perspective

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ABSTRACT

Introduction: Janus kinase inhibitors (JAKi) are anti-inflammatory medications suppressing Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway by inhibiting various cytokines receptors on the membrane of cells. Mutations and polymorphisms on JAK and STAT proteins can cause dysregulation in the balance of immune system, and ultimately result in autoimmune disorders.

Objectives: To record and summarize the overall efficacy and safety of JAKi in various autoimmune conditions such as alopecia areata (AA), psoriasis vulgaris (PV), psoriatic arthritis (PsA), atopic dermatitis (AD), vitiligo, hidradenitis suppurativa (HS), lichen planus (LP), and pyoderma gangrenosum (PG).

Methods: A thorough review of articles was performed across PubMed and Google Scholar on meta-analyses, systematic reviews, clinical trials and case studies evaluating the treatment of autoimmune disorders such as AA, PV, PsA, AD, vitiligo, LP, HS, and PG with JAKi. Duplicated data and animal experiments or in vitro/ex vivo studies were excluded.

Results: All the reviewed articles reported beneficial effects of tofacitinib and ruxolitinib application in the treatment of disorders mentioned above with the autoimmune predisposition.
Introduction

The Janus kinase inhibitors are a category of anti-inflammatory medications, targeting JAK-STAT pathways. Many inflammatory cytokines function through the JAK-STAT pathways in the human body [1,2]. Cytokines are crucial molecules working on the immune system regulation, and their dysregulation might be important in the pathogenesis of autoimmune disorders [3].

Genetic polymorphisms and different mutations can occur within JAK-STAT pathways, resulting in several forms of malignancies and autoimmune disorders, ie polymorphisms of JAK2 and STAT3 are involved in psoriasis [4]. JAKi medications provide us with the possibility of shutting down the impaired JAK-STAT pairs. Ruxolitinib and tofacitinib are the prototypes of JAKi. Ruxolitinib is a JAK1/2 selective inhibitor; it affects several parts of the innate and adaptive immune system, including natural killer cells (NKc), dendritic cells, T-helpers, and regulatory T-cells [5]. Tofacitinib preferentially blocks JAK1/3 and, to some degree, JAK2 and TYK2 [6].

JAKi, like other medications, have adverse effects (AEs) on the human body. JAKi suppress the immune system at some levels, and their consumption increases the risk of some infections such as herpes zoster (HZ). Vaccination against HZ prior to the treatment with tofacitinib is recommended. Non-HZ opportunistic infections, including cytomegalovirus, cryptoccocus, histoplasmosis and clostridium difficile are also reported in JAKi recipients [5,7].

There is a potential risk of increasing venous thromboembolism (VTE) events following the treatment with JAKi so it is recommended to avoid prescribing JAKi in patients with age >50, previous VTE, hypercoagulability, smoking, cardiovascular disease (CVD), long-term immobilization, recent trauma or surgery, paralysis, malignancy, obesity, frequent long flights, and hormonal therapy. A further consideration is required to either avoid or prescribe JAKi with extra caution in patients with a history of cancer; however, there is not enough evidence and data about the carcinogenicity of JAKi. Other AEs include anemia, reversible hyperlipidemia and minimal elevation in liver transaminases and creatine phosphokinase (CPK) [7,8].

Objectives

The development of JAKi in dermatology and rheumatology is still in the early stage; however, there is favorable evidence about the utility of JAKi in treating some of the autoimmune disorders. To prevent extensive efforts collecting data from different studies to answer specific inquiries about such disorders and medications, we performed a narrative review to summarize all the available evidence on the utility of JAKi in treating AA, PV and PsA, AD, vitiligo, LP, HS, and PG.

Methods

A thorough search was performed on PubMed, and Google Scholar using combinations of the following MeSH terms: “tofacitinib,” “ruxolitinib,” “JAK inhibitors,” “Janus Kinase inhibitors,” “alopecia areata,” “psoriasis vulgaris,” “psoriasis arthritis,” “atopic dermatitis,” “vitiligo,” “hidradenitis suppurativa,” “pyoderma gangrenosum,” “lichen planus,” “lichen planopilaris.” A total of 672 publications were found. After removing duplicates and non-suitable publications, we focused on the most recent and available pooled studies such as systematic reviews and meta-analyses and then available clinical trials, observational and case studies.

Results

Alopecia Areata

Alopecia areata is a non-cicatricial alopecia with an autoimmune etiology, affecting approximately 2% of the general population. Histopathology assessment on the involved skin showed lymphocytic infiltration around the hair follicles at the level of bulb or lower [9]. Immune system dysregulation results in hair follicles damage by T-cells and NKc. Moreover, auto-reactivation of immune cells upregulates IFN-γ and cytokines and cause further cellular damage and inflammation [10].

Excessive activation of JAK-STAT has a major effect on maintaining the activation of CD8+ T-cells and NKc. Additionally, a low level of T-regulatory cells identified in AA patients, makes it impossible to suppress excessive amounts of cytokines. These complexes of immune dysregulations contribute to hair follicles damage [10,11].

Conclusions: Tofacitinib and ruxolitinib showed potential efficacy in treating several autoimmune disorders. Based on records in the reviewed studies, both medications had acceptable safety profiles; however, physicians are recommended to outweigh the risks and benefits of such treatments for each specific condition.
Yu et al reviewed 12 studies with 346 patients. In this review 288 participants received oral tofacitinib and 58 received oral ruxolitinib. The outcome measurement was reported with the Severity of Alopecia Tool 50 (SALT 50), showing 66% overall improvement in all patients. There was no statistically difference when studies categorized by sex, age and subtypes of AA (P = 0.81, P = 0.37 and P = 0.91, respectively). The SALT 50 rates were lower in patients who received a shorter length of treatment but was not statistically significant (P = 0.25). The reported AEs were upper respiratory tract infections (URTI), urinary tract infections (UTI), herpes simplex and herpes zoster infections, alteration of blood cells count, the elevation of liver aminotransaminase and lipids; moreover, there were no fatal AEs [12]. In another meta-analysis, Hamilton et al reviewed ten different studies on the systemic and topical tofacitinib and ruxolitinib in children and teenage populations (age 1 – 17 years). The review affirmed success for JAKi in children and teens with higher numbers of complete responders and smaller numbers of poor responders compared to adults. AEs were small and limited to mild infections, diarrhea and reversible lab abnormalities [13]. In addition, Guo et al conducted a meta-analysis on 14 studies with 275 patients treating with oral and topical tofacitinib. A complete response in 54.0% and partial response in 26.1% of patients were reported. The AA relapse rates were 24.0% in the pooled results, and the main reason was medication discontinuation. A 7.2% of patients presented AEs, and the most common AE was URTI [14].

**Psoriasis Vulgaris**

Psoriasis is a chronic autoimmune inflammatory disease with the prevalence of 2% worldwide. Psoriasis has several subtypes, including plaque, guttate, inverse, and pustular. Over-activation of dendritic cells is responsible for the initial phase of psoriasis and unbalanced elevated levels of cytokines such as IL-17, IL-21 and IL-22 (mostly Th17 and IL-23 driven [15]) for the maintenance phase of inflammation. Medications such as tofacitinib and ruxolitinib targeting TNF-α, IL-23 and IL-17 and JAK/STAT pathways can be effective in treating PV [16].

Kvist-Hansen et al conducted a systematic review on five clinical trials (phase two and three trials) utilizing oral tofacitinib to treat moderate to severe forms of PV. The effectiveness was calculated based on PASI75 (Psoriasis Area & Severity Index 75% reduction). In the phase two studies, the effectiveness of tofacitinib was reported 25% with 2 mg/bid, 40.8% with 5 mg/bid, and 66.7% with 15 mg/bid compared to 2% efficacy in placebo. In the phase three studies, the effectiveness was reported 39.5% - 54.3% with 5 mg/bid and 59.2% - 81.1% with 10 mg/bid compared to 5.6% - 12.5% for the placebo recipients at weeks 16 - 24. Moreover, clinical efficacy was reported based on Dermatology Life Quality Index (DLQI) and Nail Psoriasis Severity Index (NPSI). AEs such as hyperlipidemia, CPK elevation, anemia and lymphopenia were observed in some patients [17].

Tian et al meta-analyzed seven randomized clinical trials (RCTs) about oral tofacitinib in chronic plaque psoriasis. Physician global assessment (PGA) and PASI 75 (4 studies reported PASI 90) showed denoting difference between the group of tofacitinib 5 mg/bid users and control group (P < 0.00001). The effectiveness of tofacitinib 10 mg/bid was also significantly distinct from the control group (P < 0.00001). Moreover, 5 mg/bid of tofacitinib showed less efficacy than 10 mg/bid. Even though, there was no statistically significant difference in AEs between 5 and 10 mg tofacitinib, more AEs were related to 10 mg/bid dosage [18]. Further, it is recommended to conduct clinical trials on topical types of JAKi in treating PV.

**Psoriatic Arthritis**

Approximately 19.4% of patients with psoriasis present joints involvement [19]. PsA manifestations include peripheral arthritis, enthesitis, axial disease, dactylitis, and skin characteristics [20]. No serology markers are available to distinguish PsA from psoriasis; however, hyperlipidemia, gout, axial spondylarthritis or allergic rhinitis are more common in PsA [19].

Companaro et al systematically reviewed three RCTs studying oral tofacitinib. In these studies, 947 patients treated with tofacitinib and those who only received 5 mg/bid were assessed in the review. The results at week 16 revealed a significant higher ACR20 (number of patients who achieved ≥20% response rate to the treatment based on the American College of Rheumatology Index) response than placebo. Moreover, tofacitinib also presented statistically higher ACR50, ACR70 and PASI75 response rates compared to placebo, and Health Assessment Questionnaire-Disability Index (HAQ-DI) score and post-treatment fatigue assessment showed lower rate, which means better response. Serious AEs were greater in the treatment group than the control group; however, it was not proved statistically [21].

Paik et al reviewed tofacitinib efficacy in two well-designed parallel RCTs (phase 3) in PsA patients: the OPAL Broaden with 442 patients for 12 months and the OPAL Beyond with 394 patients for six months. Patients received tofacitinib 5 or 10 mg/bid or placebo (or adalimumab 40 mg/sc combined with a csDMARD instead of placebo in OPAL Broaden) in both trials. The efficacy of tofacitinib over placebo was evaluated with ACR20, ACR50, ACR70, HAQ-DI and PASI75. After three months, tofacitinib 5 mg/bid recipients achieved statistically significant ACR20 or ACR50 and HAQ-DI

tofacitinib and ruxolitinib. All reviewed studies reported favorable safety and efficacy profiles of oral tofacitinib and ruxolitinib.

### Atopic Dermatitis

Atopic dermatitis is the most common chronic inflammatory skin disease with 3% – 10% prevalence in adults and 15% – 25% in children. Moderate-to-severe AD can alter the health-related quality of life (HRQoL) because of sleep disturbance, purities and comorbid mental conditions. Multiple inflammatory pathways and cytokines are involved in the pathogenesis of AD, and they can be considered as therapeutic targets [15,23].

Tsai et al conducted a meta-analysis on 15 RCTs and reviewed the efficacy and safety of JAKi in treating AD. Among 4,367 participants, 69 patients received topical tofacitinib 2% bid for 4 weeks, and 307 patients received topical ruxolitinib 0.15%, 0.5%, or 1.5% once daily, or 1.5% bid for 8 weeks. In the tofacitinib study, efficacy was evaluated by Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI-75%) and Body Surface Area (BSA) response. There were statistically significant higher rates of achievement to IGA, EASI-75%, and BSA responses in the treatment group compared to the control group. In assessing topical ruxolitinib among 307 patients, efficacy was evaluated by pruritus numerical rating scale (pruritus-NRS) response. Participants in the treatment group disclosed statistically greater rates of achieving pruritus-NRS response than placebo recipients. Additionally, safety was reported with Treatment-Emergent Adverse Events (TEAEs), showing a higher rate of AEs in the treatment groups that was directly related to the length of treatment (24). Further, it is suggested that topical JAKi are rational modalities in treating refractory AD; however, more clinical trials are required to evaluate the long-term safety.

### Lichen Planus

Lichen planus is a chronic inflammatory disorder that can involve derma, mucous, nail and hair follicles. The etiology of LP seems to be autoimmune with the incidence rate of 2% – 3% [30]. The overactivation of CD8+ T-cell lymphocytes and dysregulation of CD4+ T-cells have been observed to play a major role in the pathogenesis of LP [30].

Damsky et al 2020 evaluated the benefit of oral tofacitinib in a case series of three patients with erosive lichen planus (ELP). Treatment with oral tofacitinib 5 mg/bid was initiated for all patients. Additional therapy with methotrexate and prednisolone was added to the therapeutic regimen of patient #1 due to the refractory course of his condition. All patients showed dramatic improvements and complete or near-complete remission while they were on tofacitinib. Discontinuation of tofacitinib in patient #1 resulted in ELP relapse even when he continued methotrexate and prednisolone. Re-initiation of tofacitinib 5 mg/bid resulted again in improvement in patient #1. Tofacitinib was tolerated well with no reported AEs in any of the cases [31].

Another case series by Yang et al reported the effectiveness of oral tofacitinib in ten patients with refractory lichen planopilaris (LPP). Treatment with tofacitinib 5 mg/bid for 8 patients and 5 mg/tids for the other 2 patients,
with more severe disease, was commenced and continued for 2 – 19 months. Disease activity assessed by LPP activity index (LPPAI), and showed statistically significant improvement compared to pre-treatment (P = 0.0014). One patient reported hair loss upon treatment discontinuation (due to weight gain), which stabilized when medication was re-started with a 5 mg/bid dosage [32]. A significant efficacy and low AEs were reported in the reviewed case series. Large-scale and long-term studies are required to assess the safety and efficacy of the treatment.

**Hidradenitis Suppurativa**

Hidradenitis suppurativa is a chronic inflammatory disorder in 1% of general population [33,34]. Pathogenesis of HS starts with cutaneous changes around hair follicles and dysregulation of innate and adaptive immunity: elevated levels of ILs following the overactivity of T-helpers, ultimately affect neutrophils, macrophages and plasma cells. These changes result in a vicious cycle of inflammation, pain, purulence, tissue destruction, and disfiguring scars [33-36]. JAKi suppress the impacts of ILs, and thus they can be a potential treatment for HS; however, limited studies aim to prove the benefit of JAKi in treating HS.

Savage et al reported two cases of HS treating with oral tofacitinib 5 mg/bid: a patient treated for one year and the other patient for three years. Both patients showed favorable results: patient #1 was pain and drainage free after 11 months. Upon discontinuation at 12 months, the modest disease activity was observed, and tofacitinib re-treatment directed the disease to full remission. Patient #2 experienced gradual remission over 3 years of treatment. At this time, localized herpes zoster infection was reported which was controlled with intravenous valacyclovir. No other AEs were reported in either of the two patients [35].

**Pyoderma Gangrenosum**

Pyoderma gangrenosum is a rare, ulcerative and painful dermatological condition with a multifactorial pathogenesis. Diagnosis of PG is clinical after excluding other causes ie infection, neoplasia, thrombophilia, and other inflammatory conditions. PG often is related to other systemic inflammatory conditions [37-40]. Pathophysiology of PG is not entirely known; however, it represents dysregulation of the innate and adaptive immune systems: neutrophil dysfunction, JAK2 mutation, overexpression of integrin and dysregulation of integrin signaling, and overproduction of ILs seems to be involved in the course of PG [41].

There are few studies about the efficacy of JAKi in treating PG; however, few case reports show potential benefits that need further large-scale RCTs. In a case report, Choi et al presented a patient with a history of cocaine abuse and 10-month PG lesions refractory to other forms of treatment, including adalimumab, tacrolimus, prednisolone, and rituximab. Treatment was transitioned to oral tofacitinib 5 mg/bid: significant improvement was observed after two weeks, and 95% improvement and sustained remission were reported at three months post-treatment [42].

Another case report was conducted by Kochar et al presenting three patients with refractory PG. The first two patients were treated with 5 mg of tofacitinib twice daily, and no signs of disease activity and AEs were reported after 12 months. The third patient commenced on tofacitinib 5 mg/bid and concomitant steroid, and his PG lesions were improved but not healed entirely within a month. Then steroid was stopped, and tofacitinib up-titrated to 10 mg/bid and improvement continued [43]. Reviewed studies indicated the effectiveness of oral tofacitinib in the treatment of PG; however, more studies with larger scales are needed to assess the accuracy of this allegation.

**Conclusions**

Tofacitinib and ruxolitinib showed potential efficacy in the treatment of several autoimmune disorders. Based on a thorough review of the literature, it is concluded that both medications have acceptable safety profiles; however, physicians are recommended to outweigh the risks and benefits of the treatment for each specific condition. Further, there are not enough data and studies about the benefit and safety of tofacitinib and ruxolitinib in treating disorders such as HS, PG, and L.P. We predict that JAKi will be utilized more broadly in treating autoimmune disorders, and future reviews can be a paradigm guideline helping clinicians to treat their patients.

**Acknowledgement**

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**References**


Introduction: Efficient interpretation of dermoscopic images relies on pattern recognition, and the development of expert-level proficiency typically requires extensive training and years of practice. While traditional methods of transferring knowledge have proven effective, technological advances may significantly improve upon these strategies and better equip dermoscopy learners with the pattern recognition skills required for real-world practice.
Objectives: A narrative review of the literature was performed to explore emerging directions in medical image interpretation education that may enhance dermoscopy education. This article represents the first of a two-part review series on this topic.

Methods: To promote innovation in dermoscopy education, the International Skin Imaging Collaborative (ISIC) assembled a 12-member Education Working Group that comprises international dermoscopy experts and educational scientists. Based on a preliminary literature review and their experiences as educators, the group developed and refined a list of innovative approaches through multiple rounds of discussion and feedback. For each approach, literature searches were performed for relevant articles.

Results: Through a consensus-based approach, the group identified a number of emerging directions in image interpretation education. The following theory-based approaches will be discussed in this first part: whole-task learning, microlearning, perceptual learning, and adaptive learning.

Conclusions: Compared to traditional methods, these theory-based approaches may enhance dermoscopy education by making learning more engaging and interactive and reducing the amount of time required to develop expert-level pattern recognition skills. Further exploration is needed to determine how these approaches can be seamlessly and successfully integrated to optimize dermoscopy education.

Introduction

As a visual specialty, dermatology relies on the recognition of characteristic features and patterns within clinical and dermoscopic images of skin lesions. Other fields in medicine, such as radiology and pathology, also rely on pattern recognition to formulate diagnoses and plans of care. In these fields, experts are distinguished from novices by their speed and accuracy in interpreting medical images and completing diagnostic tasks. While analyzing images of skin lesions, viewers may perform global interpretation, which encompasses holistic processing with immediate pattern recognition. Viewers may also perform feature search, which involves the identification of specific features (e.g., dermoscopic criteria) associated with normalcy or pathology.

Experts and novices differ in the order that they perform these mental processes during medical image analysis. Novices usually start by attempting to search deliberately for features and comparing their findings with their prior, albeit limited, knowledge and experiences. In contrast, experts typically reach a diagnostic conclusion relatively quickly through global interpretation and then seek to justify their conclusion with an efficient feature search.

Visual diagnostic skills at the expert level require the ability to perform global interpretation—or efficient pattern recognition without deliberate search strategies. Traditional educational methods that primarily drill declarative knowledge (e.g., specific features) have been largely ineffective in teaching novices the pattern recognition skills required for real-world practice. With these conventional training modalities, expert-level proficiency in dermoscopy has typically required extensive training and years of practice. A diagnostic accuracy study performed among medical students and healthcare providers estimated that at least six years of experience may be necessary to develop a sufficient level of competency [1].

The container model embodies a traditional instructional approach centered on the idea that the acquisition of knowledge is comparable to filling one mind, or one mental filing cabinet, with as many facts and concepts as possible [2,3]. This learning theory was developed on the metaphor of our minds acting as containers capable of accumulating and retaining different items, whether real or metaphorical [4]. Using this metaphor, knowledge is regarded as a commodity to be transferred from one medium to another [3].

The expectation that diagnostic concepts can be placed in a fixed cognitive “container,” where they can then be easily accessed, is misleading, especially in the setting of medical education. The successful recall of knowledge in the real-world context seems to be strongly influenced by the learning context [5]. However, knowledge acquired using the container model is usually isolated from its context and thus static and inflexible. In practice, knowledge, even if highly case-specific, is not a readily available object to retrieve but something to reconstruct and adapt when faced with different situations [2].

Thus, opponents to the container model point out that in solving new problems, learners who have diligently absorbed declarative knowledge (e.g., facts and concepts that can be verbalized) under the container model may still fail to appropriately retrieve and apply that knowledge [6]. Alternatively, learners may be able to successfully adapt their knowledge in the problem-solving process, but this successful retrieval and application may require a high cognitive load [6].

The cognitive load theory is an instructional theory derived from current understanding of cognitive architecture [7]. The term cognitive load refers to the learner
ment of mental bandwidth to complete tasks [7]. It is based on the idea that working memory—where information is stored temporarily—has limited capacity to store and use new information [7]. As a result, if the amount of new information exceeds mental capacity, further learning and accurate decision making will be impaired [8]. It is important for educators to consider cognitive load when designing instructional materials to maintain the overall load within the optimal range for learning and performance.

For difficult tasks, learners may primarily rely on deliberate and purposeful thinking, and this process may strain their working memory, negatively affecting their ability to complete the tasks. In cognitive psychology, the dual process theory recognizes two thought systems: slow (deliberate) thinking and fast (automatic) thinking [9]. For medical image interpretation, the dual process theory manifests as a two-component diagnostic strategy in which the fast system facilitates pattern recognition and the slow system facilitates analytical reasoning [10]. Within a medical simulation, accessing relevant knowledge and skills while assessing the simulated clinical environment may create a high extraneous cognitive load for learners, causing poor performance [8]. The high cognitive load experienced by learners in medical simulations may be explained by their extensive use of slow thinking as opposed to fast thinking, the former requiring considerable mental effort and use of mental resources.

Fast thinking, or non-analytical reasoning, is a key component of expert performance for diagnostic tasks that rely on pattern recognition, such as skin lesion classification in dermatology and X-ray interpretation in radiology [11]. For image interpretation education, an important goal is for novices to gradually develop a degree of automaticity in pattern recognition, which translates to a low cognitive load [10]. Traditional teaching methods based on the container model have been generally ineffective in both teaching flexible knowledge and training automaticity in novices.

In dermoscopy education, educators who use the container model usually provide instruction to passive learners on a defined set of diagnostic features, adding to their “containers.” In teaching learners to detect the relative presence or absence of a feature, this approach in effect requires real-world stimuli to likewise fit a binary interpretation (e.g., present/absent, melanoma/non-melanoma). However, real-world stimuli frequently present on a continuum, or a sliding scale, where concerning features may be completely non-existent, obviously present, or extremely subtle.

Dermoscopy education requires instructional approaches that transfer flexible knowledge on the continuous nature of features and their clinically relevant contexts. This review seeks to explore an array of emerging theory-based approaches in image interpretation education that may displace the container model and enhance dermoscopy training programs.

Objectives

This article represents the first of a two-part review series on novel instructional approaches in image interpretation education that could translate to dermoscopic educational interventions. In this first part, we will present a collection of theory-based approaches—such as whole case learning, microlearning, perceptual learning, and adaptive learning—that could enhance dermoscopic image interpretation education. While these emerging directions may also apply to general dermatology education, the scope of this series is limited to dermoscopy education.

Methods

To promote innovation in dermoscopy education, the International Skin Imaging Collaborative (ISIC) assembled a 12-member Education Working Group that comprises international dermoscopy experts and educational scientists. For this initiative, the group convened virtually on a regular basis to discuss novel methods in medical image interpretation education that could be translate to dermoscopy training programs. Based on a preliminary literature review as well as their experiences as educators, the group developed and refined a list of innovative approaches through multiple rounds of discussion and feedback.

For each approach, literature searches were performed in the PubMed and Google Scholar databases for relevant English-language articles. Search strategies included terms for concepts of dermoscopy education, image interpretation education, and health science education in addition to the instructional approach under investigation. Articles published since 2000 were preferred for inclusion, but articles published before 2000 were also considered, especially when seeking to understand the historical and theoretical underpinnings of some approaches. Additional articles were identified among the references of retrieved articles and through discussions with educational scientists.

Relevant literature findings on the educational theories, methods, and concepts identified during the consensus process are presented in this review series. The theory-based approaches described in the first part of this series include: whole-task learning, microlearning, perceptual learning, and adaptive learning.

Results

Whole-Task Learning (4-C/ID)

Overview

Whole-task learning is a time-efficient instructional design in medical education that teaches complex skill development
through authentic clinical scenarios [12]. For learners, spontaneous transfer of knowledge from the learning situation to the clinical environment is challenging [13]. Through incorporation of real-life problems and fragmentation of instruction, whole-task learning aims to teach foundational knowledge in a way that fosters the “transfer out” of knowledge to actual practice. This approach also seeks to facilitate skill transfer in a manner that attends to cognitive load [12].

A specific whole-task learning strategy is four-component instructional design (4-C/ID). The four components in 4-C/ID are: (1) learning tasks, (2) supportive information, (3) just-in-time information, and (4) part-task practice [12]. Learning tasks, which function as the backbone of 4-C/ID, are authentic tasks sequenced from simple to complex in terms of difficulty and organized into “task classes.” Supportive information may be presented at the beginning of a task class and provide foundational knowledge. Just-in-time information may be provided right when the learner needs it for a specific task. Part-task practice is an optional component in which the learner is given the opportunity to practice a specific task in order to develop a degree of automaticity. By shifting the focus of learning from lectures to clinical scenarios, learners may better appreciate the educational content and its relevance to their professional roles [14].

Whole-task learning is similar to case-based learning in that both emphasize realistic clinical situations in the instructional design. In case-based learning, learners engage in group-based discussions of authentic patient cases and receive guidance and feedback from instructors [15]. Learners are usually expected to prepare on their own through self-directed learning in advance of the case-based learning sessions [15]. In whole-task learning, learners are presented with authentic clinical scenarios prior to receiving formal instruction. As learners navigate the scenarios, they are provided further information relevant to the scenarios in a structured delivery format.

Applications in Medical Education

Task-based learning has been applied in surgical education in recent years. A randomized controlled study conducted among surgical interns implemented task-based learning in an inanimate surgical skills laboratory setting [16]. Compared to the control group, the intervention group performed better on post-intervention assessments and required less time to complete the clinical procedure [16]. Another qualitative study evaluated the feasibility and efficacy of whole-task learning in a web-based doctoral-level pharmacotherapy course and garnered positive results [14]. Learners expressed that by posing authentic scenarios, the complex delivery format provided them an opportunity to identify with their future health profession [14].

Applications in Dermoscopy Education

In whole-task learning, authentic scenarios, structured in a way to facilitate skill transfer to clinical encounters, serve as the framework for learning. This approach contrasts with conventional teaching models that focus on didactic lectures, which are then supported by hypothetical scenarios. Whole-task learning could be applied to dermoscopy education to promote problem-solving skills and foster professional independence. Learning tasks may involve addressing skin complaints in hypothetical patient encounters. Learners then receive instruction on the dermoscopic appearance of common dermatologic diagnoses (supportive information).

Dermoscopic training programs that involve case-based learning could be adapted to whole-task learning by re-structuring the curriculum with cases at the forefront and re-imagining each case as a series of learning tasks [17]. For example, dermoscopic cases are introduced prior to receiving instruction. As they navigate through cases, learners may receive further information on specific dermoscopic features and management approaches in the form of didactic lectures, multimedia content, or other teaching materials [18]. After completing the didactic portion, learners may then engage in repetitive practice to develop task automaticity and efficiency.

Microlearning

Overview

Microlearning is an instructional approach that involves segmenting the curriculum into short bursts, or small bites, of learning [19]. In contrast to traditional training sessions with “massed” practice, microlearning sessions may involve spaced review and distributed practice, increasing on-task attention and decreasing mind wandering [20]. According to the “forgetting curve,” memory retention declines over time as learners tend to forget much of their learned material within hours or days [19]. Microlearning seeks to address this trend by introducing and re-introducing lessons in short bursts. Through distributed practice, microlearning promotes the transfer of information from short-term to long-term memory storage [19].

With the microlearning approach, learners experience low cognitive load since working memory does not become overstrained, and this maintains learning capacity [21]. In reducing mental fatigue, this strategy increases learning retention and efficiency [19]. While microlearning lessons are usually self-paced, learners tend to complete them faster given their high level of engagement [19].

Applications in Medical Education

In recent years, microlearning modules have become more readily available to learners with the emergence of
multimedia content that can be easily accessed via personal devices. In a Dutch non-randomized study involving medical and biomedical university students, investigators employed an open-source mobile application (or “app”) to teach circulation and respiration using microlearning and spaced review [22]. For a month before the exam, learners used the app to complete training modules with practice assessments that reviewed educational content and provided feedback. Intensive app users performed significantly better on the final exam compared to moderate users and non-users, though these results may also be correlated with increased time spent learning [23].

Applications in Dermoscopy Education

In dermoscopy education, a real-life example of microlearning can be found in a telementoring framework model called Project ECHO (Extension for Community Health Outcomes) [24]. As an effective alternative to on-site mentoring, tele-mentoring allows learners to process the cases with real-time guidance from dermoscopy experts [25]. In Project ECHO, teaching sessions occur on a monthly basis and pair a didactic micro-lecture with learner presentations of real-life challenging cases encountered during patient care. A before-and-after study among primary care providers demonstrated that ECHO attendance increased participants’ ability to interpret dermoscopic images of skin cancer [25].

Another example of microlearning in dermoscopy can be found in the educational webcasts posted by the International Dermoscopy Society (IDS). These webcasts include short YouTube videos of 5 to 10 minutes in length organized into disease-based learning (Level 1), morphology-based learning (Level 2), and context-based learning (Level 3) as well as case-based learning [26]. To facilitate conceptual understanding, these webcasts could be expanded by posting dermoscopic images with practice questions plus key points in a microlearning format on a weekly or monthly basis.

Since microlearning can be applied to drill certain topics or specific skills, educators may consider whether to implement “blocked” or “interleaved” practice. Many programs involve “blocked” practice in which the learner practices specific skills (eg A, B, C) one at a time in isolation (eg AAA BBB CCC) [27]. An alternative to “blocked” practice is “interleaved” practice in which learners practice multiple different skills in an intermixed order (eg ABC BCA CAB). In interleaved practice, the amount of practice devoted to a specific skill becomes spaced, or distributed, across the learning session [27].

By continuously exposing learners to multiple relevant topics, interleaved practice may be more effective in preparing learners for real-life applications. In dermoscopy education, a microlearning module in which learners exclusively practice diagnosing seborrheic keratosis (SKs) would result in blocked practice, while one requiring a learner to distinguish between SKs, benign nevi, and melanomas, presented in a random order, would result in interleaved practice. In a before-and-after study for a dermoscopy training program, blocked practice for benign lesions resulted in high specificity for benign lesions but poor sensitivity for malignant lesions in that participants would frequently categorize melanomas as, for instance, SKs [28]. Sensitivity for malignant lesions subsequently improved with the adoption of interleaved practice [28].

By segmenting complex tasks into smaller units, microlearning represents a powerful teaching tool for dermoscopy education. It may enable an efficient transfer of expert-level pattern recognition skills to novices, especially when implemented through technology tools such as smartphone apps. In bridging the gap between formal and informal learning, the use of microlearning technology may enhance learner engagement and motivation as well as knowledge retention [29]. Microlearning modules may also be suitable for gamification in which game design principles are applied to enhance the learning experience and activate intrinsic reward pathways.

Perceptual Learning

Overview

Perceptual learning is a learning method that challenges the container model theory by promoting the idea of experience as fundamental to developing expertise [30]. In neuropsychology, perceptual learning refers to the changes that occur in neural circuitry as a result of experience, resulting in the development of sensory discrimination [31]. This phenomenon explains how we learn to discriminate between faces, speech sounds, and musical pitches. For visual discrimination training, this approach relies on repeated exposures to numerous stimuli (eg visual features) so that one learns to perceive subtle differences between the stimuli. The concept of perceptual learning may be applied to visual specialties in which the educator teaches key diagnostic features and then creates opportunities for learners to practice recognizing these features with feedback.

For medical image interpretation education, the two components of perceptual learning are discovery and fluency [6]. In the discovery phase, students learn to identify new information relevant to the diagnostic task by ignoring less relevant information and extracting the more salient points. Using inattentional selectivity, learners may process a large amount of information from a case. Fluency comes with practice and refers to the student ability to efficiently recognize the information needed for diagnostic tasks.
Applications in Medical Education

Through perceptual learning, learners receive exposure to real-life examples, engage in repetitive practice, and gradually learn to recognize important diagnostic features quickly and accurately. Perceptual learning has been applied to radiology and electrocardiogram (EKG) image interpretation training, where learners have demonstrated gains in accuracy and fluency [6,30]. More recently, perceptual learning has been applied to dermatology education, where learners classify clinical images of rashes and skin lesions by morphology, configuration, and distribution [32]. Through perceptual learning, learners demonstrated the ability to quickly and accurately identify skin lesion characteristics at a level comparable to that of expert dermatologists.

Applications in Dermoscopy Education

In a dermoscopy training program for primary care providers, educators applied a heuristic training approach that resembled the discovery phase of the perceptual learning approach [33]. In the heuristic strategy, learners are expected to devise their own heuristics, or mental shortcuts, for future decision-making based on their experiences. Following an introductory didactic training session on classical dermoscopic features, learners in the heuristic training arm were provided the opportunity to view a series of dermoscopic images with minimal guidance from instructors. Labeled with the diagnosis only, these images did not contain further annotation or description, and learners were expected to discover salient features on their own. On post-intervention assessments, learners in the heuristic training arm performed as well as learners who had received feedback on the salient features in those images.

Adaptive Learning

Overview

Adaptive learning is an educational approach that optimizes learning for the individual learner through innovative technology tools [6]. This approach features an adaptive algorithm that tailors the individual learning sequence according to their strengths and weaknesses. Adaptive algorithms resemble an automated form of the deliberate practice strategy commonly used to achieve expert performance in music and sports. In deliberate practice, a teacher evaluates student performance and recommends practice activities (training tasks) and practice objectives (training goals) based on the teacher prior experiences and the student needs [34]. Students follow teachers recommendations, practice with full concentration, and receive or self-generate immediate feedback [34].

In traditional medical education, pre-determined lecture or training schedules could not be easily adapted or modified to accommodate the individual student needs [35]. Students may have different starting points for a given topic, or they may learn at different paces based on their individual abilities and the instructional method being used. Adaptive approaches represent a solution to these problems: by responding to the learner response times and accuracy rates, adaptive algorithms can repeat content, or adapt content difficulty, to optimize the learning process [36].

Adaptive response time-based sequencing (ARTS) is an example of an adaptive learning approach that customizes the learning sequence based on performance data [37]. Once the algorithm has detected mastery of a specific concept according to objective learning criteria, it can retire that concept and shift to focus on the learner weaker areas. Learning criteria should correlate with a given level of proficiency and could involve a number of accurate responses provided within a specified amount of time, correlating with a degree of automaticity. Training is considered complete when all criteria are met.

Applications in Dermoscopy Education

Adaptive algorithms have been successfully applied in teaching transesophageal echocardiography (TEE) image interpretation. Like dermoscopic image interpretation, TEE interpretation involves recognition of diagnostic patterns. In one teaching method, an algorithm modified the sequence of and time intervals between different TEE cases to suit each learner needs [38]. It evaluated both response speed and accuracy to determine whether to retire or re-sequence a specific concept. This method proved effective in improving response time and accuracy and optimizing performance for TEE learners.

For electrocardiography (EKG) interpretation, adaptive learning has also been successful in promoting content mastery. Reading an EKG, like evaluating a skin lesion in dermoscopy, requires pattern recognition skills that novices are expected to obtain via experiential learning [30]. With ARTS, the pace of learning was adapted for each EKG learner based on response time and accuracy. As with the previous example, a concept was retired only if the learner achieved the target response time while maintaining accuracy. If both measures were not achieved, the concept was re-sequenced into the learning sequence.

Applications in Medical Education

For dermoscopy education, adaptive algorithms may gradually increase the difficulty of dermoscopic images based on learner performance to generate faster improvements in performance. Alternatively, if a learner repeatedly fails to recognize a specific dermoscopic feature, additional images containing the feature may be shown until the learner starts to “see” the feature. Since learners encounter new content according to a personalized training schedule, demotivation
We envision a hypothetical dermoscopy training program that combines the strengths of each approach presented in this article. In this program, learning concepts, such as a specific dermoscopic diagnosis, would be organized as their own unit. Each unit may be prefaced by a real-world clinical scenario that promotes whole-task learning. Educational content on the dermoscopic diagnosis (eg clinical presentation, dermoscopic appearance) could then be presented via microlearning modules that deliver instruction in small segments to minimize extraneous cognitive load.

Each microlearning module may also include multiple example images of each diagnostic feature plus new cases for perceptual learning. These example images and cases could be hosted on a user-friendly application that contains elements of game design and provides immediate feedback to learners. Adaptive learning algorithms built into the application would either re-sequence or retire cases according

Conclusions

A summary of the instructional approaches explored in the first part of this review series is included in Table 1. In general, training programs that apply microlearning modules, perceptual learning cases, and/or adaptive learning algorithms may enable novices to acquire expert-level knowledge in an effective manner. Meanwhile, whole-task learning equips learners for real-life clinical situations using hypothetical clinical scenarios.

Table 1. Summary of the educational theories presented in the first part of this review series plus examples of existing or potential applications in dermoscopy education.

<table>
<thead>
<tr>
<th>Educational Theory</th>
<th>Description</th>
<th>Application(s) in Dermoscopy Education</th>
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| Container Model    | • Learners receive passive instruction and fill their mental “container” with as many facts and concepts as possible.  
• Acquired knowledge is usually static and inflexible because it is isolated from its context. | **Existing Applications**  
• didactic lectures  
• rules-based algorithms |
| Whole-Task Learning | • Curriculum design is based on authentic clinical scenarios and comprises 4 components: (1) learning tasks, (2) supportive information, (3) just-in-time information, and (4) part-time practice. | **Potential Application**  
• curriculum design: structured as a series of clinical scenarios based on real-life cases |
| Micro-learning     | • Educational content is segmented into short bursts, or small bites, of learning that may be spaced apart.  
• This approach is expected to enhance engagement, increase knowledge retention, and decrease mental fatigue. | **Existing Application**  
• Project ECHO, developed by dermatology faculty at MaineHealth |
| Perceptual Learning| • For medical image interpretation, fine visual discrimination skills are developed through repeated exposures to numerous examples of important visual features.  
• With feedback and practice, novices may learn to efficiently extract important features and ignore irrelevant ones. | **Existing Applications**  
• YouDermoscopy, created and developed by Meeter Congressi  
**Potential Applications**  
• library of training cases: learners classify hundreds of images and receive feedback on performance |
| Adaptive Learning  | • Adaptive algorithms respond to the individual performance data and make personalized modifications to the training schedule.  
• Each individual training schedule is tailored to his/her strengths and weaknesses in order to optimize learning outcomes. | **Potential Applications**  
• learning modules: learners complete assessments; adaptive algorithms retire specific learning concepts based on objective mastery criteria |

ECHO = Extension for Community Healthcare Outcomes.
to learner performance, indicated by response time and accuracy. Upon completion of all microlearning modules for the unit, learners are offered the opportunity to revisit the clinical scenario from the beginning of that unit.

To evaluate the impact of these educational approaches on dermoscopic image interpretation skills, educators may assess learner performance at multiple time points using validated instruments that measure both fluency and accuracy in diagnosing lesions. Investigators may also perform prospective audits of clinical diagnoses versus histopathological diagnoses among participants in the training program.

With the container model, learners were taught to interpret images using a given set of diagnostic features and/or rule-based algorithms. However, learners often struggled with manipulating and acquiring applied knowledge to new images. Compared to traditional methods, emerging approaches in image interpretation education are more interactive and learner-centered. These approaches may improve learning outcomes by grounding learning in real-life clinical scenarios (whole-task learning) or delivering instruction in short segments (microlearning). For dermoscopic training, perceptual learning and adaptive learning may be especially valuable in that they provide immediate feedback and adapt the pace of learning to learner performance, respectively. The second part of this series will continue exploring instructional strategies and methods in image interpretation education that could also support dermoscopy education.

References


Instructional Strategies to Enhance Dermoscopic Image Interpretation Education: a Review of the Literature

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ABSTRACT

Introduction: In image interpretation education, many educators have shifted away from traditional methods that involve passive instruction and fragmented learning to interactive ones that promote active engagement and integrated knowledge. By training pattern recognition skills in an effective manner, these interactive approaches provide a promising direction for dermoscopy education.

Objectives: A narrative review of the literature was performed to probe emerging directions in medical image interpretation education that may support dermoscopy education. This article represents the second of a two-part review series.
Introduction

Curricular requirements for medical education emphasize the importance of teaching students how to apply acquired knowledge in solving problems and exercising critical judgment [1]. The ability to manipulate knowledge in this manner is difficult if declarative concepts (e.g., key terms and definitions) are rigid and decontextualized. In the preclinical phase of medical education, learning often entailed attending organized lectures and memorizing isolated facts specific to the organ systems under study [2]. In light of the evolving educational environment, this traditional structure is being supplanted as educators incorporate classroom technology tools and experiment with different approaches (e.g., group discussions, case presentations, patient contact experiences) [2].

These emerging approaches aim to integrate knowledge across different specialties while improving long-term retention and preparing learners for real-world practice. In medical education, an instructional approach that promotes integrated knowledge is the illness script theory, derived from schema theory. In psychology, “schemas” are bundles of pre-existing knowledge structures in long-term memory, where information is stored indefinitely, and “scripts” refer to those knowledge structures representing generic event sequences that can be retrieved from long-term memory and activated in the appropriate real-world context. For instance, conceptual knowledge pertaining to a specific illness can be quickly retrieved upon recognition of associated triggers, such as a set of symptoms [3]. In contrast with the container model introduced in the first part of this series, the illness script theory promotes integration of declarative knowledge and pattern recognition and reinforces the development of clinical reasoning skills [3].

In image interpretation education, recent shifts away from the container model as the dominant instructional approach have occurred in radiology education [4]. Radiograph interpretation represents a complex skill since learners must apply their knowledge of anatomy and pathology and their problem-solving skills to assess each image and reach a diagnosis or conclusion [5]. In addition to absorbing relevant declarative knowledge, learners must restructure and adapt their knowledge for each new image [4]. In radiology education, traditional teaching methods have been gradually replaced by more interactive approaches, such as case-based instruction [6]. Here learners are engaged as problem solvers, actively processing and integrating information [6].

As with radiology education, pathology education has also demonstrated similar shifts away from conventional approaches in favor of more interactive ones [4, 5]. Through an integrated pathology curriculum, learners become more active in their own learning, and pathology more integrated with other medical subjects [7]. As a result, acquired knowledge is more flexible and primed for application across multiple different contexts.

Similar educational methods that confer conceptual understanding and train pattern recognition through real-life cases represent a promising new direction for dermatoscopy education. Combined with developments in technology, these reflect contemporary trends in teaching strategies in medical education. This review seeks to explore an array of emerging instructional strategies in image interpretation education that could meaningfully support dermatoscopy training programs.

Objectives

This article represents the second part of a two-part review series on instructional approaches in image interpretation education that may translate to dermatoscopy education. The first part of this series discussed limitations of traditional approaches based on the container model and considered contemporary learning theories including whole-task learning,
microlearning, perceptual learning, and adaptive learning. In this second part, we will explore instructional strategies and methods—such as gamification, social media, perceptual and adaptive learning (PALMs), metacognition, and productive failure—that may also support dermoscopy education. While these strategies and methods could apply to general dermatology education, the scope of this series is limited to dermoscopy education.

Methods

The methods employed for our literature review are described in detail in the first part of this series [8]. This article presents additional instructional strategies identified during the group consensus and literature search processes of this study. The instructional strategies presented in this second part include: gamification, social media, perceptual and adaptive learning modules (PALMs), metacognition, and productive failure.

Results

Gamification

Overview

In gamification, principles of game design are strategically applied to the learning environment to enhance motivation and engagement. This strategy is derived from motivation theory, which emphasizes the importance of individual motivation in the learning process [9]. Motivation is defined as the process by which goal-directed activities are initiated and sustained [10]. In games, factors shown to enhance player motivation include challenge, curiosity, autonomy, fantasy, competition, collaboration, and recognition [10]. Conveniently, many of these factors may be incorporated into educational games to make the learning process more engaging.

By taking advantage of familiar game mechanics and dynamics, games in the educational setting induce goal-directed activity in an artificial social context, producing quantifiable outcomes [11]. The pursuit of clearly defined goals in games has been associated with increased affective measures and decreased cognitive load [12]. In other words, students have more fun when learning in a gamified environment, where they also benefit from the ability to control their own learning process.

Game Design Elements

To invoke a sense of challenge and novelty among learners, educators may incorporate the following classical elements of game design: avatars, points, badges, performance graphs, and leaderboards [11]. Avatars are digital representations of the player within the game and may be as simple as a customizable icon chosen by the player. Points are numerical representations of the player progress, and badges are emblems of achievements that can be earned and collected. For instance, a player may earn a badge for reaching a specified number of points or completing activities. Both points and badges provide immediate feedback and function as rewards. Finally, performance graphs display a player performance over time, focusing on improvements.

Each of the above elements are highly personalized aspects of the player experience that serve to sustain learner motivation [13]. By providing clear feedback, many of the elements may also enhance self-regulated learning in which learners control their own learning process and monitor their own performance. The performance data generated by player activity enables educators to analyze learner performance in order to optimize the educational program.

Applications in Dermoscopy Education

In dermoscopy education, educational applications (or “apps”) such as YouDermoscopy (developed by Meeter Congressi in Italy), DermaChallenge (developed by a team from the Medical University of Vienna in Austria), and DiagnosUs (developed by Centaur Labs in the U.S.) have all embraced a gamified approach [14-16]. The YouDermoscopy app divides dermoscopic cases into different levels that can be unlocked and provides feedback on learner performance, such as through point rewards [14]. Targeted towards dermatologists, DermaChallenge features quizzes containing dermoscopic images, and for each image, players select the corresponding diagnosis from choices representing common dermoscopic diagnoses [15]. If incorrect, players receive immediate feedback and review the correct answer. Quizzes are similarly organized into multiple levels that players may unlock.

More broadly, the DiagnosUs app allows players to practice image interpretation for dermoscopy in addition to other specialties, such as radiology, ophthalmology (retinography), and obstetrics/gynecology (ultrasound) [16]. While the app contains other noteworthy features such as crowd-based labeling, its educational component is mainly geared towards medical learners, and the dermoscopy section primarily covers melanoma detection training [16]. Quizzes, called “missions,” may contain dermoscopic images of nevi that players classify as benign or malignant. Once players submit their answer, they can review the correct answer, see the number of users who answered correctly or incorrectly, and participate in the discussion forum for that case [16].

Social Media

Overview

With the pervasiveness of social media in daily life, educators are also seeking to leverage social media platforms to enhance curriculum design, promoting classroom interaction.
and facilitating peer-to-peer learning [17]. Educators may use these platforms to either deliver or complement curriculum delivery. As active participants, learners may contribute discussion points and comments and collaborate with peers via group chats. These interactions may occur in either a synchronous fashion with real-time responses or an asynchronous fashion with delayed responses.

Applications in Medical Education

In a study in China, investigators evaluated the feasibility of a social networking platform called Microblog among pharmacotherapy students [18]. Learners completed pharmacotherapy case studies through Microblog, and the end-of-course survey results indicated that a majority of learners agreed that the platform enhanced their learning experience by increasing their active engagement in the course. Some shared that compared to meeting face-to-face, meeting online was more convenient, allowing team members to collaborate from any location “with a simple click”[18] However, some still expressed a preference for face-to-face communication, citing issues such as delayed responses and online chatter. Instructors needed to balance between maintaining a discreet online presence to promote student participation and monitoring discussion threads for potential issues (eg wrong/misleading information, repetitive comments).

Ideally, social media platforms in the educational setting create opportunities for students to share ideas and learn from peers [19]. An example in radiology education is a de novo social media platform called Collective Minds Radiology (developed by a team in Sweden) [20]. Available to download as a smartphone app, this platform enables users to share their expertise and collaborate on challenging radiology cases [20].

While the development of these platforms de novo may be time-consuming and labor-intensive, the incorporation of existing platforms into the learning environment represents an alternative route. For example, an online research methodology course implemented a collaborative space on the Twitter platform to enhance student engagement [21]. In this course, students discussed topics of interest on Twitter through tweets (text-based posts constrained by 140-280 characters) and course-specific hashtags (indexed keywords or phrases preceded by the “#” symbol). A significant majority of learners in this study agreed that the collaborative groupwork via the social media platform positively contributed to their learning.

Applications in Dermoscopy Education

As an online platform for dermatologists to discuss interesting dermoscopic cases, the International Dermoscopy Society (IDS) forum represents an example of social media in dermoscopy education [22]. Here users can share their opinions for cases (eg dermoscopic features, dermoscopic diagnoses, treatment plans) and provide their rationale, sometimes supported by references. By facilitating academic discussion, the forum allows users to learn from each other and enables new ideas to emerge. Similarly, the IDS Facebook group offers another virtual space for users to network and discuss interesting cases [23].

On Instagram, a popular photo- and video-sharing app, the handle for the most popular dermoscopy account is “@dermoscopy_.” Managed by a team of dermatologists in Brazil, the account boasts over 40,000 followers. The content producers frequently post short educational videos and dermoscopic images with the diagnoses or answers in the captions. Many dermatology residency programs also employ group text messaging apps such as WhatsApp and GroupMe. In these virtual spaces, trainees may share interesting de-identified dermoscopic cases from their training experiences and solicit ideas from attending physicians and other trainees.

Many educational apps that incorporate elements of game design also benefit from social media features. These apps may present cases in a game-like format and then incorporate a forum for users to discuss the cases. For example, the “Play Live” function on the YouDermoscopy app allows players to provide an opinion or request assistance from others in real-time [14]. The DiagnosUs app also has a discussion forum for each case that players may use to ask clarifying questions and share their findings [16].

While the advantages of social media include increased learner engagement through opportunities for collaboration, its incorporation into the learning environment may require administrative training and technical support [17,25]. To ensure a high-quality learning experience, administrative staff may need to routinely monitor online activity to ensure accuracy of information and provide further guidance as needed.

Perceptual and Adaptive Learning Modules (PALMs)

Overview

Perceptual and adaptive learning modules (PALMs) represent a novel teaching tool in medical education that combines the strengths of both perceptual learning and adaptive learning in order to accelerate expertise [26]. As discussed in the first part of this series, the perceptual learning technique is an interactive approach that introduces a specific visual feature and then exposes learners to numerous examples so that learners can quickly and accurately identify that feature in new cases [27]. The adaptive learning technique optimizes learning outcomes through continuous performance tracking and personalized modifications [28]. This method equates low response times and high accuracy rates with content mastery [28].

The combination of these two approaches in PALMs has the potential to transform education in medical fields that rely on pattern recognition skills. Learners using PALMs may be asked to classify a number of images from a training library after being introduced to a specific visual feature. Adaptive algorithms analyze their individual performance — as assessed in terms of response time and accuracy — and make personalized modifications to their future training [29]. Learners continue training until they achieve content mastery, demonstrated by their fulfillment of the objective learning criteria. Through this training method, learners develop expert-level pattern recognition skills in an efficient manner while learning how to perform relevant clinical tasks. While the perceptual learning and adaptive learning approaches can be applied individually, learning outcomes seem to be optimized when they are strategically combined.

Applications in Medical Education
In transesophageal echocardiography (TEE) and electrocardiography (EKG) interpretation education, PALMs have enabled learners to develop pattern recognition skills comparable to those of experts. In a non-randomized controlled study on TEE interpretation, anesthesiology residents completed PALMs that showed about 180 video clips, provided feedback, and measured response time and accuracy [30]. Compared to both their baseline and the control group, learners in the PALM group performed significantly better in terms of accuracy and fluency after six months. In another before-and-after study on EKG interpretation, learners used PALMs containing over 400 unique EKG tracings and similarly retained accuracy and fluency gains after one year compared to their baseline [31].

In dermatology education, PALMs have also been successful in training pattern recognition, as demonstrated in a before-and-after study among medical students [32]. For different visual features, the PALMs presented example images in a flashcard style and measured response time and accuracy. As learner performance improved, images from that category were spaced further apart to assess long-term retention.

Applications in Dermoscopy Education
PALMs may be developed for dermoscopy education in which educators teach key dermoscopic features for common dermatologic diagnoses and then expose learners to numerous example images for each feature. Learners practice identifying features on new images and receive feedback, while adaptive algorithms measure response times and accuracy rates and retire specific learning concepts based on objective mastery criteria. To promote optimal learning, the number of example images required for these modules remains to be explored. A study on radiograph interpretation found that reusing images was similarly effective to only using unique images in terms of learning outcomes [33]. While an extensive number of unique example images may thus not be necessary for PALMs, components that seem essential include opportunities for immediate feedback and repetitive practice.

Metacognition
Overview
Metacognition, a term originally coined in the 1970s, refers to the awareness of one’s own cognitive processes, or cognition about cognition [34]. In medical education, learners who apply metacognition reflect on their study strategies and learning outcomes and correct errors in order to improve performance [35]. In becoming more aware of their learning processes, students may strategically allocate their learning efforts and simultaneously reduce their cognitive load. As medical knowledge and healthcare systems continue to evolve, providers must be able to continually assess their own knowledge, performance, and possible biases to maintain good clinical practice in a rapidly changing world [36].

Applications in Medical Education
While metacognitive processes may be difficult to measure given their complexities, researchers have developed various instruments to evaluate metacognition and self-regulation, the latter referring to the ability to control one’s own learning through planning, monitoring, and evaluation [36]. In the literature, the following methods have been adopted for medical education:

1. The Metacognitive Awareness Inventory (MAI) measures two broad categories of metacognition, knowledge of cognition and regulation of cognition [37].
2. The Inventory of Learning Styles (ILS) measures aspects of self-regulation, external regulation, and lack of regulation [38]. The self-regulation scale measures the degree to which students reflect on their learning processes, identify the cause of their learning problems, and manage their efforts in achieving their own learning objectives. The external regulation scale measures the degree to which students rely on didactic aids, such as formal learning objectives, and external support, such as feedback and assignments from instructors. The lack of regulation scale concerns the inability of students to regulate learning and the perceived lack of external support.
3. The Self-Regulated Learning Perception Scale (SRLPS) measures motivation and action to learning; planning and goal setting; strategies for learning and assessment; and lack of self-directedness [39].

The above instruments may be employed on a routine basis to gain further insight into metacognitive processes and learning experiences. For example, a study on metacognition across four medical schools employed both the MAI
and SRLPS and found that students in the clinical phase of their training demonstrated higher levels of metacognition, especially in terms of planning and goal setting, compared to those in the preclinical phase [39]. Students enrolled at schools that applied learner-centered teaching methods, such as problem-based learning, also displayed higher levels of metacognition compared to those learning via conventional methods [39]. Similar scales may be employed in dermoscopy education to assess changes in metacognitive awareness over the course of a training program.

Applications in Dermoscopy Education

A proposed strategy to prime metacognitive awareness in dermoscopy learners involves prospective judgments of learning (JOLs) in which learners rate how likely they would remember an item on a test [40]. The act of making JOLs has been shown to enhance long-term memory and improve learning performance on cued recall tests [41]. In dermoscopy education, this strategy may be applied by prompting learners to rate their level of confidence in answering a question, such as whether a dermoscopic image contains a specific feature. Learners may track changes in their performance as well as changes in their confidence throughout the training program in order to better understand their strengths and weaknesses.

Metacognition allows learners to more actively engage in their own learning as they consider their knowledge, personal abilities, and learning strategies [42]. To better understand their strengths and weaknesses for metacognitive processes, learners require some form of feedback on their performance. Digital solutions, such as mobile apps, may facilitate metacognitive awareness through auto-generated displays of performance data, encouraging proactive adjustments of learning strategies. In incorporating elements of game design, the process of reflecting on learning progress may become more engaging for both learners and educators.

Beyond the classroom setting, learners may also contemplate instances of cognitive error in real-life clinical practice. Cognitive errors specific to skin cancer diagnosis include inattentional blindness (overlooking a melanoma) and diagnostic error (evaluating a melanoma but incorrectly diagnosing it as a benign skin growth). When presented with feedback and performance data, learners may reflect upon errors in their learning strategies and adjust accordingly.

In real-life clinical practice, most expert dermoscopists describe systematically capturing dermoscopic images of all biopsied lesions and then reviewing those images when their clinical diagnosis is discordant with the histopathologic diagnosis. In reviewing the images, overlooked clues may be identified, improving the provider proficiency. Metacognitive awareness thus has the potential to improve performance and long-term learning outcomes in the clinical setting.

Productive Failure

Overview

Productive failure is a relatively novel concept in education that uses early failures to activate retrieval of prior knowledge and promote problem-solving skills [43]. It plays on the proverbial wisdom of failing before succeeding and encourages creative risk-taking [44]. This method is conceptualized as a two-phase process [43]. In the first phase, learners are given a challenging problem to solve on their own or in groups prior to any, or minimal, didactic training (Generation and Exploration). After struggling to generate their own solutions to the challenging problem, learners are provided formal training (Consolidation and Knowledge Assembly). The learner initial struggle with the challenging problem may facilitate conceptual understanding and meaningful future learning [45]. Learners who are prepared for future learning demonstrate the ability to apply key learning concepts in solving new problems [45].

By inducing early failures within a safe learning environment, productive failure may create conditions in which learners become more motivated to obtain and retain a solution to the problem given the effort already invested into solving it [46]. This phenomenon is known as the endowment effect: once learners endow a problem with resources, such as time and effort, it may become more emotionally valuable to know and learn the solution [46].

In a testing-oriented learning environment, instructional design that incorporates productive failure may also benefit from the testing effect, which refers to the positive effects of test-taking on long-term memory and knowledge retention [47]. While the challenging problem is not necessarily presented as a test, students may perceive it as a form of assessment as they practice retrieving their prior knowledge. Though these difficult exercises may hamper learning performance in the short run, they may improve learning outcomes in the long run [48].

Applications in Medical Education

In implementing the productive failure approach, it is important that students actively generate mistakes themselves rather than observe the mistakes of others [49]. Yet, the productive failure approach may be uncomfortable for learners with strong aversion to failure. To minimize negative psychological consequences of failure, instructors may apply a classroom strategy called error management training in which errors are framed as “positive” occurrences and natural byproducts of the learning process [50]. In a randomized study, medical students assigned to error management training were encouraged to probe freely, make errors during ultrasound practice, and reflect on their errors [50]. In a simulation-based test conducted a week later with real patients, students in the error management arm performed better than those in the error avoidance arm.
Conclusions
A summary of the instructional strategies and methods explored in the second part of this review series is included in Tables 1 and 2. Over the years, many dermoscopy educators may have intuitively adopted these approaches in response to learner feedback, personal observations, and changes in the learning environment. In dermoscopy education, the strategic integration of these emerging approaches may support the development of pattern recognition skills, such as global interpretation and holistic processing.

In light of our review, we envision a hypothetical dermoscopy training program with active learning strategies informed by contemporary learning theories. In this program, learning concepts, such as a specific diagnosis, could be organized as their own unit, and each unit could be prefaced by a challenging problem that simulates productive failure and activates problem-solving processes. For each diagnosis, learners could learn and review educational content using PALMs that teach key diagnostic features and expose Technology tools may also ease learners aversion to failure by creating a low-stakes learning environment, allowing students to explore new problems in a safe and non-threatening setting. The use of technology enables small failures to be “contained and managed” within an external system [44].

Applications in Dermoscopy Education
Productive failure recognizes the inherent value of mistakes and the educational utility of errors. By inducing early failures within a safe learning environment and activating the problem-solving process, productive failure can be an effective teaching tool. In dermoscopy education, productive failure can be implemented by providing challenging cases before each module, followed by feedback and guidance. This will help activate a shift towards planning and goal-setting and probe metacognitive awareness of potential weaknesses. Incorporation of technology tools may also help establish a safe learning environment that permits learners to make mistakes and understand their mistakes, spurring them towards later success in their learning journey.

Table 1. Summary of the instructional methods presented in the second part of this review series plus examples of existing or potential applications in dermoscopy education.

<table>
<thead>
<tr>
<th>Educational Method</th>
<th>Description</th>
<th>Application(s) in Dermoscopy Education</th>
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| Gamification       | • Factors that contribute to learner motivation include challenge, curiosity, autonomy, fantasy, competition, collaboration, and recognition.  
• In gamification, principles of motivation theory and elements of game design are applied to the educational context to enhance learner engagement and promote goal-directed learning. | **Existing Applications**  
• YouDermoscopy, created and developed by Meeter Congressi SRL  
• DermaChallenge (Dermonaut), created by H. Kittler, P. Tschandl, and C. Rinner  
• DiagnosUs, created and developed by Centaur Labs |
| PALMs              | • PALMs combine both perceptual learning techniques and adaptive learning algorithms to efficiently train pattern recognition skills.  
• Learners classify unique images and receive immediate visual feedback, and adaptive algorithms determine whether to re-sequence or retire specific learning concepts. | **Potential Application**  
• dermoscopy PALMs:  
  • educators teach key diagnostic features and expose learners to numerous example images  
  • learners identify features on new images and receive feedback  
  • adaptive algorithms retire specific learning concepts based on objective mastery criteria |
| Social Media       | • Social media platforms are leveraged by educators to increase learner engagement and foster peer-to-peer interaction.  
• Learners benefit from opportunities for collaboration on cases plus the convenience of a web-based platform.  
• Disadvantages may include delayed responses, poor quality of interaction, and wrong or misleading information from peers. | **Existing Applications**  
• IDS Forum  
• Facebook pages (e.g., IDS page)  
• Instagram accounts (e.g., @dermoscopy_)  
• WhatsApp groups (e.g., dermatology trainee groups) |

IDS = International Dermoscopy Society; PALMs = perceptual and adaptive learning modules.
learners to numerous example images. Learners identify features on new images and receive feedback, and adaptive algorithms retire specific learning concepts based on objective mastery criteria. The PALMs may involve elements of game design such as points and badges that enhance learner engagement.

The program could also be supplemented by group forums, hosted either in-person or on social media platforms, where learners collaborate with their peers on challenging cases. Using real-time feedback and performance data from multiple components of the course, learners may apply metacognitive processes to identify strengths and weaknesses and modify their learning strategies.

This hypothetical program represents just one way to apply active learning strategies in dermoscopic image interpretation education. For a complex multi-component program, technical challenges are to be expected, but existing technology tools, such as virtual delivery formats and smartphone apps, may represent smart solutions to these challenges. As medical educators seek to apply innovative methods to dermoscopy education, the development of appropriate technology will support the seamless integration of multiple methods.

Collectively, these emerging approaches in image interpretation education illuminate an exciting direction for the future of dermoscopy education. Compared to traditional approaches, these strategies may enable the dermoscopy learner to develop expert-level pattern recognition skills more effectively. PALMs may be especially valuable in that they provide immediate feedback and adapt the training schedule to the individual’s performance. The development of technology tools that enable the integration of these different approaches in dermoscopy education will greatly facilitate endeavors to optimize knowledge acquisition and skills development.

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### Table 2. Summary of the educational concepts presented in the second part of this review series plus examples of existing or potential applications in dermoscopy education.

<table>
<thead>
<tr>
<th>Educational Concept</th>
<th>Description</th>
<th>Application(s) in Dermoscopy Education</th>
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</table>
| Metacognition       | • Learners who apply metacognition (awareness of one’s own cognitive processes) reflect on their learning processes and learning outcomes.  
                      • When presented with visual feedback and performance data, learners may identify potential errors in their learning strategies and adjust accordingly. | Potential Application  
                      • JOLs: learners “bet” on whether they will remember a given item or rate their level of confidence in answering a question (e.g., whether a dermoscopic image contains a specific feature) |
| Productive Failure  | • Learners are given a challenging problem to solve prior to didactic training (Exploration). After struggling to generate their own solutions, learners are then provided the didactic training (Consolidation).  
                      • The learner initial struggle with the challenging problem facilitates meaningful future learning. | Potential Applications  
                      • challenging problem: learners annotate dermoscopic images prior to instruction  
                      • error management: learners receive instructions that frame errors as positive occurrences |

JOLs = judgments of learning.


**SARS-CoV-2 Vaccination and Chilblain-like Lesions: What Do We Know so Far?**

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**ABSTRACT**

**Introduction:** The coronavirus pandemic has caused massive damage to global health care and the economy. The vaccination program has been paced around the globe to return as soon as possible to pre-COVID time. Although all the vaccines have been approved after the rigorous clinical and safety trials, some adverse effects have surfaced and are being reported from different parts of the world. One such side effect is chilblain-like lesions following the COVID vaccination. Chilblain lesions, also known as pernio, are an inflammatory condition usually affecting the acral regions of the body. It is mostly reported from cold and damp areas and has multiple causes associated with it.

**Objective:** This study aims to review the publicly available data and to provide concise and comprehensive information as well as evaluate the potential pathology, clinical approach, and management of CLL post-vaccination.

**Methods:** An extensive literature search over PubMed, Cochrane library, Google Scholar, and Clinicaltrails.gov from inception till 5th October 2021, without any restriction of language was carried out. All the recruited articles were reviewed, and their bibliographies were also screened for any relevant information.

**Results:** 12 studies (10 case reports and 2 case series) were retrieved reporting the incidence of CLL post-vaccination. 8 studies reported incidence in female patients while 5 reported in males, with one study mentioning no gender. Moreover, most of them were either from Europe or the United States of America, except for two cases, reported from Turkey.

**Conclusions:** Although the overall incidence of Chilblains following COVID-19 vaccination is low, there is still a strong need to find out the exact mechanism behind this to redefine the safety and administration criteria of the vaccines and to formulate a proper management protocol.
Introduction

In December 2019, a zoonotic RNA virus SARS-Cov-2 was isolated in a Chinese patient. The disease caused by it was termed COVID-19 that has spread at an enormous rate throughout the globe [1]. The high infectivity rate and asymptomatic transmission have caused the quick spread leading to a pandemic [2].

The body requires time to respond to the viral attack; hence symptoms usually develop 2 to 14 days post-exposure, typically presenting with fever, cough, dyspnea, fatigue, amnesia, and ageusia [3,4]. In acute conditions, there are incidents of hemoptysis and ground-glass opacities [5]. While SARS-CoV-2 mainly causes respiratory diseases, clinicians have noticed other handful of extrapulmonary manifestations [6,7].

The only way to restore routine life is to speed up the vaccination programs. All the currently available vaccines underwent rigorous trials and were approved after demonstrating an acceptable safety profile[8]. The most common post-vaccination adverse effects are pain at the injection site, fatigue, and chills. However, these effects are transient [9]. However, some severe side-effects have been reported as well including splanchnic venous thrombosis [10] and vaccine-induced immune thrombotic thrombocytopenia [11]. There is a need to address them since reports of adverse events have been regarded as one of the leading motives behind vaccine hesitancy in low- and middle-income countries (LMICs) [12].

One recently reported adverse event attributed to the COVID-19 vaccine is Chilblain or Chilblain-like lesions, illustrated in Figure 1. Chilblain (pernio) is an inflammatory condition, histologically characterized by dermal edema with perivascular lymphocytic infiltrates, caused by exposure to non-freezing, and cold conditions. It is clinically characterized by bluish-purple papules on acral surfaces, as shown in Figure 2. The causes vary from idiopathic acrosyndrome and Raynaud’s phenomenon to systemic diseases such as autoimmune disorders, and rarely in Epstein-Barr virus (EBV) [13–15].

Objectives

This study aims to review the publicly available data and to provide concise and comprehensive information as well as evaluate the potential pathology, clinical approach, and management of CLL post-vaccination.

Methods

Here, we scrutinize the association between coronavirus vaccines and post-vaccination CLL by performing an extensive literature search over PubMed, Cochrane library, Google Scholar, and Clinicaltrials.gov from inception till 5th October 2021, without any restriction of language. To achieve comprehensive results, the keywords used in the search string included “SARS-CoV-2 Vaccine”, “Coronavirus Vaccine”, “Corona Vaccine”, “COVID-19 Vaccine”, “COVID Toes”, “Chilblain”, “Pernio”, “Blue toes”. The terms were separated by BOOLEAN operators “OR” and “AND”. All the recruited articles were reviewed, and their bibliographies were also screened for any relevant information. Ultimately, 12 studies (10 case reports and 2 case series) were retrieved, tabulated in Table 1. This review evaluates the potential pathology, clinical approach, and management of CLL post-vaccination.

Figure 1. Chilblain-like lesions post vaccination. (A) Purpuric patches on the marginal side of fingers [17] (B) Non-painful violaceous lesions on the big toe, the third toe and the fourth toe [78].
It is established that the Angiotensin-converting enzyme2 (ACE2) serves as a cell receptor mediating the entry of SARS-CoV-2 with the help of transmembrane protease serine 2 (TMPRSS2). This process downregulates ACE2 in cells since it is removed from the external membrane site [21]. Although it allows the entry of the virus into the cell, ACE2 also provides a vaso-protective function by converting Angiotensin II to Angiotensin (1-7). High levels of Angiotensin II lead to endothelial dysfunction and results in vasoconstriction and activation of immune cells and cytokines [22]. It is hypothesized that binding of coronavirus spike proteins leads to shedding and loss of protective function of ACE2 receptor, since Angiotensin (1-7) cannot be formed, and leads to accumulation of Angiotensin II at the tissue level [23]. Similarly, we hypothesize that the spike proteins produced by mRNA (Moderna and Pfizer) and adenovirus vaccines (AstraZeneca) leads to the accumulation of Angiotensin II, by inhibiting the action of ACE2, leading to endovascular damage.

Another proposed mechanism for CLL post-vaccination is the excess of interferons. The way mRNA vaccines may trigger CLL is by increasing interferon-alpha. Upon entry into the cell, the ssRNA and dsRNA are recognized in the cytosol by endosomes and then take part in the innate immune response. Endosomal Toll-like Receptors (TLR) bind to ssRNA in the endosome, while the components of inflammasome bind to ssRNA and dsRNA in the cytosol resulting in INF-1 production alongside multiple inflammatory mediators [24,25]. Although mRNA vaccines are encoded with nucleotides to reduce binding to TLR and reduce high levels of interferon, there might be some unknown pathology, responsible for excessive production of INF-1.

Similarly, the adenovirus vaccine once injected causes innate immunity activation by stimulating macrophages. It engages multiple pattern-recognition receptors, especially TLR9, to induce INF-1 production [25].
<table>
<thead>
<tr>
<th>Author</th>
<th>Age, Sex</th>
<th>Country</th>
<th>Vaccine Administered</th>
<th>Previous Medical History</th>
<th>Presenting Complaint</th>
<th>Days from vaccination to onset of symptoms</th>
<th>Significant examination and Investigations finding</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davido et al [78]</td>
<td>41, F</td>
<td>France</td>
<td>Pfizer-BioNTech-162b2</td>
<td>Bipolar disorder, for which she was taking valproate for &gt;10 years.</td>
<td>Sudden toe pain with walking impairment and itching at night, chilblain-like skin</td>
<td>4 days after first dose</td>
<td>Physical examination revealed non-tender, violaceous toes of the left foot. WBC= 70 mmol/L CRP= 1 mg/L anti-Spike (S) antibodies= 0.642 UI/ml</td>
<td>Apixaban and low-dose aspirin until circulating immune complexes were obtained &lt;3 μg Eq/ml after 14 day</td>
<td>Recovered after 150 days</td>
</tr>
<tr>
<td>Piccolo et al [79]</td>
<td>41, F</td>
<td>Italy</td>
<td>Pfizer-BioNTech-162b2</td>
<td>Not significant</td>
<td>Painful, chilblain-like lesion on the volar aspects of the second and the third fingertip of right hand</td>
<td>24 hours after second dose</td>
<td>High levels of IgG anti-spike antibodies, determining the positive response to the vaccine.</td>
<td>Oral cinnarizine (75 mg twice per day)</td>
<td>Recovered after one month</td>
</tr>
<tr>
<td>Cameli et al [20]</td>
<td>60, N/A</td>
<td>Italy</td>
<td>Pfizer-BioNTech-162b2</td>
<td>Not significant</td>
<td>Pernio-like lesions on both hands, accompanied by itching and burning sensation</td>
<td>14 days after second dose</td>
<td>Physical examination showed erythematosus-violaceous patches and swelling on the fingers. Occasional appearance of livedo reticularis-like manifestations on the lower limbs.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lesort et al [30]</td>
<td>82, F</td>
<td>France</td>
<td>Pfizer-BioNTech-162b2</td>
<td>History of psoriasis and has been on methotrexate for &gt;10 years</td>
<td>Slightly painful lesions on both hands and feet</td>
<td>24 hours after first dose</td>
<td>Physical examination revealed macular violaceous and erythematos lesions of the fingers and toes.</td>
<td>Topical clobetasol cream, second vaccine dose, she developed chilblain-like lesions again after second dose that were treated similarly.</td>
<td>Recovered</td>
</tr>
<tr>
<td>Author</td>
<td>Sex</td>
<td>Age, Sex</td>
<td>Country</td>
<td>Vaccine Administered</td>
<td>Significant examination and investigations finding</td>
<td>Presenting Complaint</td>
<td>Days from vaccination to onset of symptoms</td>
<td>Treatment</td>
<td>Outcome</td>
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</tr>
<tr>
<td>Holmes et al [31]</td>
<td>F</td>
<td>48, F</td>
<td>USA</td>
<td>Moderna</td>
<td>Allergic contact dermatitis to fragrances and positive antinuclear antibodies.</td>
<td>Single chilblain-like papules overlying the joint spaces of the hands and feet.</td>
<td>10 days after the first dose</td>
<td>Initial dermatology evaluation was recommended.</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td>Meara et al [32]</td>
<td>F</td>
<td>33, F</td>
<td>USA</td>
<td>Moderna</td>
<td>Mild persistent asthma, regular user of inhaled corticosteroid.</td>
<td>Painless new onset blue and purple nodules on the tips of 3 fingers and 2 toes.</td>
<td>1 week after her first dose</td>
<td>Laboratory workup was unrevealing.</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Lopez et al [33]</td>
<td>M</td>
<td>64, M</td>
<td>USA</td>
<td>Pfizer-BioNTech-162b2</td>
<td>Not significant</td>
<td>Violaceous skin discoloration for 10 days that started on the left hallux and gradually spread to all toes on the bilateral feet.</td>
<td>3 days after second dose</td>
<td>Antibodies and blood tests were negative.</td>
<td>N/A</td>
</tr>
<tr>
<td>Pileri et al [80]</td>
<td>M</td>
<td>42, M</td>
<td>Italy</td>
<td>Pfizer-BioNTech-162b2</td>
<td>Not significant</td>
<td>Nonpainful erythematous-to-violaceous patches located on the hands and nail bed.</td>
<td>12 days after first dose</td>
<td>Dermatological examination revealed mildly pruritic, violaceous plaques and nodules on the dorsal hands.</td>
<td>Topical corticosteroids and antihistamines</td>
</tr>
<tr>
<td>Temiz et al [17]</td>
<td>M</td>
<td>44, M</td>
<td>Turkey</td>
<td>CoronaVac</td>
<td>Not significant</td>
<td>Chilblain-like lesions on the dorsal hands.</td>
<td>7 days after the vaccine</td>
<td>Erythematous-violaceous patches on the dorsal hands.</td>
<td>Topical corticosteroids and antihistamines</td>
</tr>
<tr>
<td>Temiz et al [17]</td>
<td>M</td>
<td>53, M</td>
<td>Turkey</td>
<td>CoronaVac</td>
<td>Not significant</td>
<td>Chilblain-like lesions on the dorsal hands.</td>
<td>7 days after the vaccine</td>
<td>Chilblain-like lesions on the dorsal hands.</td>
<td>Topical corticosteroids and antihistamines</td>
</tr>
</tbody>
</table>

Table 1 continues...
<table>
<thead>
<tr>
<th>Author</th>
<th>Age, Sex</th>
<th>Country</th>
<th>Vaccine Administered</th>
<th>Previous Medical History</th>
<th>Presenting Complaint</th>
<th>Days from vaccination to onset of symptoms</th>
<th>Significant examination and Investigations finding</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connie Kha, MD et al [34]</td>
<td>70, F</td>
<td>USA</td>
<td>Moderna</td>
<td>Pityriasis lichenoides chronica (PLC), which remained clinically stable with clobetasol 0.05% ointment</td>
<td>Pruritic papular rash on the digits of her right hand. Associated symptoms were pain with movement of the right proximal interphalangeal joints of the 4th and 5th digits that resolved on 10th day.</td>
<td>2 days after first dose</td>
<td>Physical examination revealed a few lesions located on the extensor surfaces of the extremities. A complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, Sjögren antibodies (anti-SS-A/anti-SS-B), and antinuclear antibody were either within normal limits or negative.</td>
<td>Clobetasol 0.05% ointment twice daily.</td>
<td>Recovered, however got the same rash 3 days after second dose.</td>
</tr>
<tr>
<td>Nebreda et al [81]</td>
<td>N/A, F</td>
<td>Spain</td>
<td>Moderna</td>
<td>Not significant</td>
<td>Itchy edematous erythematous papules on the back of the hands and fingers and erythematous spots in palms</td>
<td>N/A</td>
<td>Superficial perivascular lymphocytic infiltrates with vascular damage and red cell extravasation, with Papillary dermal oedema</td>
<td>Topical corticosteroids and lesions</td>
<td>Recovered</td>
</tr>
<tr>
<td>Nebreda et al [81]</td>
<td>N/A, F</td>
<td>Spain</td>
<td>Moderna</td>
<td>Not significant</td>
<td>Itchy edematous erythematous lesions in fingers</td>
<td>N/A</td>
<td>Deep perivascular lymphocytic infiltrates surrounding the sweat glands. Papillary dermal oedema was also present</td>
<td>Topical corticosteroids and lesions</td>
<td>Recovered</td>
</tr>
<tr>
<td>Nebreda et al [81]</td>
<td>N/A, M</td>
<td>Spain</td>
<td>Moderna</td>
<td>Not significant</td>
<td>Itchy edematous erythematous lesions in fingers</td>
<td>N/A</td>
<td>Superficial perivascular lymphocytic infiltrates</td>
<td>Topical corticosteroids and lesions</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

CBLL = chilblain-like lesions; CRP = C-reactive protein; F = female; M = male; N/A = Not available; USA = United States of America; WBC = white blood count.
The common histological finding in the included cases was perivascular lymphocytic infiltrate. This finding is in line with that of Boada et al.[35], where Idiopathic Pernio had 89% of cases having the same histopathology. In Connie Kha et al. [34] immunohistochemical demonstrated the presence of CD31 T cells. This hammers up the finding by Cribier et al [18], where they presented how chilblains have predominant T-lymphocytic infiltration, with only a few B cells. Mild superficial edema was also seen in Meara et al [32]. Holmes et al [31] highlighted the case of a patient with the presence of interstitial eosinophils. In the case by Lesort et al [30] blood vessel endothelial cells of the mid dermis were also seen as a prominent structure. This was also seen in a previous study. While working on the histology of COVID-19 associated pernio, Recalcati et al [36] observed 14 cases, that had a prevalent perivascular pattern, and signs of endothelial activation. Detailed biopsy reports of included studies are summarized in Table 2. While there exists, much research describing the histopathological finding in different types of chilblains, the ones occurring after COVID-19 vaccination is still unclear. Hence, leaving room for potential working. Figure 4 shows how CLL appears histopathologically in hematoxylin–eosin–safron stain.

**Diagnosis**

The criterion for CLL diagnosis is unestablished and differs between physicians. Some recommend history and examinations to be sufficient while others prefer going for laboratory testing, including CBC, cold agglutinins, antinuclear antibodies, and cryoglobulins. Some even prefer skin biopsy.
Table 2. Histopathological findings of included cases.

<table>
<thead>
<tr>
<th>Author</th>
<th>Procedure</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesort et al [30]</td>
<td>Skin Biopsy</td>
<td>partly necrotic epidermis overlying a dense dermal lymphocytic infiltrate forming rather well-circumscribed aggregates around blood vessels, eccrine sweat glands and occasionally nerves (Figure 4). The endothelial cells of the blood vessels of the mid dermis were occasionally prominent.</td>
</tr>
<tr>
<td>Holmes et al [31]</td>
<td>Skin Biopsy</td>
<td>psoriatic and spongiotic dermatitis with superficial and deep perivascular lymphocyte-predominant inflammation as well as numerous perivascular and interstitial eosinophils. There was no evidence of vasculitis.</td>
</tr>
<tr>
<td>Meara et al [32]</td>
<td>Skin Biopsy</td>
<td>Superficial and mid-dermal perivascular cuffed lymphocytic infiltrate. Mild superficial dermal edema is present. No inter-face changes are present. There is no evidence of vasculitis or vasculopathy.</td>
</tr>
<tr>
<td>Lopez et al [33]</td>
<td>Punch Biopsy</td>
<td>Superficial and deep infiltrate of lymphocytes around vessels and eccrine glands, with papillary dermal oedema. No thrombi or vasculitis are seen.</td>
</tr>
<tr>
<td>Connie Kha et al</td>
<td>Punch Biopsy and Immunoc</td>
<td>Dense and predominantly perivascular lymphocytic infiltrate within the superficial-to-deep reticular dermis. The epidermis appeared normal with no vacuolar changes at the epidermal-dermal junction. There was a notable papillary dermal edema. Within the superficial dermis, some vessels exhibited slightly thickened walls with trophism of lymphocytes, although vascular wall hyalinization, neutrocytosis, or intravascular thrombi were not evident. Immunohistochemical analysis demonstrated a majority of CD3+ T cells in the lymphocytic infiltrate.</td>
</tr>
<tr>
<td></td>
<td>hemocytometric analysis</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Skin biopsy of the lesion. (A) Necrotic epidermis and a dense dermallymphocytic infiltrate. (B) aggregation of infiltrates around blood vessels. (C) infiltration around sweat glands (Stain: haematoxylin–eosin–saffron stain) [30]
Moreover, one study demonstrated dermoscopy usage to evaluate background vessels and additional features [37].

Cappel et al. studying patients at Mayo Clinic recommend following a systemic approach, starting from history and physical examination to ordering labs and skin biopsy for those with advanced disease [14].

Clinical Management

Some literature suggests no treatment plan for chilblains, as it resolves itself [38]. Whilst some recommend treatment with avoidance of cold and damp conditions. Many studies are determining potential therapeutic measurements in cases of severe disease [15, 39]. Pharmacologically, calcium channel blockers, such as nifedipine, are reportedly helpful in relieving the condition [16, 40-42].

Herein, we summarize and present a systematic approach to a patient with such lesions based on the current data and treatment plans that worked for patients presented in Table 1.

Exposure

Previously, these lesions were supposed to be caused and aggravated by a cold environment [15, 43]. Even though the etiology in post-COVID-19 vaccine CLL is not linked to the weather, physicians, dealing with such cases, may consider the environment as an aggravating factor, as depicted in the cases from colder countries, hence preventing cold weather shall be chosen as a first-line management plan. Moreover, adding on heat provision may also improve symptoms drastically, as proposed by Nyssen et al [15].

Corticosteroids

Topical corticosteroids remained the choice of management in four cases [17, 31–33]. However, despite widespread usage, the level of clinical evidence suggesting it is a possible treatment measure is insufficient [39, 44]. Souwer et al compared the efficacy of topical betamethasone vs placebo to treat chilblains and no significant differences were perceived [44]. However, Mayo Clinic demonstrated their efficacy, benefitting 6 of 8 patients [14]. This supports the treatment plan followed in included cases. Nevertheless, the contradiction in trial results and actual benefits received by the patients requires a thorough and strong evaluation. Moreover, the cases lack reporting of adverse effects that may have occurred as a result of steroids, hence clinical work in this aspect is crucial.

Calcium Channel Blockers

Calcium channels induce the inhibition of calcium entry into the cells, hence playing a vital role in vasodilation. Since vasoconstriction due to cold is one of the presumed pathophysiology for chilblains, calcium channel blockers have been long debated for their efficacy in CLL. Numerous trials and works have been done in this area. Of them all, Nifedipine has been widely recognized, with trials comparing its effect with placebo [45], diltiazem [46], topical 5% minoxidil [47, 48], and topical glyceryl trinitrate [49], proving its superiority to them. However, it is still a conflicting treatment option as Souwer et al showed that there was no difference in results in placebo versus nifedipine [50].

In the case of chilblains following COVID-19 vaccination, none of the case reports included in this review (Table 1) used it as a treatment regimen, the plausible reason being the etiology was considered different. However, medicines, that increase blood flow to affected organs have been recommended and used in CLL following COVID-19 infection [38]. Hence, this may highlight the fact that calcium channel blockers can play an important role in vaccine-induced lesions as well. Nevertheless, strong research data are required to connect the dots.

Topical Nitroglycerin

This drug, having the same effects as that of calcium channel blockers, acts by releasing free radical NO, hence relaxing smooth muscles and increasing the blood flow [51].

Topical nitroglycerine (0.2%) showed improvement in outcomes of Chilblains in a study by Verma P et al [52]. Moreover, a case report by Weingarten et al [53], used it as a treatment option for COVID-19 induced CLL and found it effective. However, the first study tested a small sample group (22 patients), while the case only used it for one patient, hence, more work on a greater sample size can be done in the area to weigh the efficacy of this option.

Pentoxifylline

This drug works by improving the red blood cell flexibility by increasing erythrocyte ATP and cyclic nucleotide levels. Current evidence goes in the favor of this option [54]. In the trial by Noaimi, 18% of patients showed improvement in symptoms when treated with pentoxifylline compared to only 27.2% in the group taking prednisolone 0.5mg/kg and topical clobetasol ointment [55]. Another research by Al-Sudany NK et al showed a significant improvement in lesion healing compared with placebo [56]. Moreover, Assimakopoulos et al proposed how this option can be used to resolve other severe complications of COVID-19, highlighting the possible efficacy of this drug [57].

Based on this, pentoxifylline can be considered a part of the treatment plan in patients with CLL.

Hydroxychloroquine

This drug is often used as a first-line treatment in several autoimmune diseases [58]. In a retrospective study by Yang et al, four of five perniosis patients responded well to
Hydroxychloroquine [59]. This can be due to their underlying anti-inflammatory action, which results from their interference with antigen processing in macrophages and other antigen-presenting cells [60].

Acupuncture

In a study by Xiang et al, in 2005, the acupuncture group, combined with massage, showed a 100% effective rate for CLL treatment compared to 76.6% in medicine [61]. Acupuncture is an old Chinese alternative medicine practice, which works by inserting needles into the body, to improve blood flow. While there are reservations to alternative medicine, based on this study, more trials should be performed to verify and to check this therapeutic line of management for CLL.

Temiz et al [17] used antihistamines as a management option, however, there are insufficient data to evaluate their efficacy in CLL; hence, more studies are needed in this regard.

Other cutaneous Manifestations of COVID-19 Vaccines

During the vaccines trial, the typical adverse cutaneous reactions were local injection site reactions while erythema, induration, and tenderness, were specifically reported in the Moderna phase III trial [62]. However, as the vaccines entered the real world, diverse cutaneous adverse events have been documented. Mazza et al [63], reported case series, comprising three cases of purpuric eyelid lesions following the Pfizer vaccine, which may be a manifestation of vaccine-induced microangiopathy. Similarly, in another case, the patient experienced urticarial rash along with a flare-up of his previously well-controlled atopic dermatitis [64]. Morbilliform rashes [65,66], urticaria [67,68], pityriasis rosea [68,69], lichen planus [70], and many other cutaneous reactions following COVID-19 vaccination are present in the literature. Notable is the fact that women comprised the majority, which may help draw a relation between any sex-linked reactions. Nevertheless, a thorough evaluation is the need of time to establish complete links [17].

Chilblains like Lesions Following COVID-19 Infection

While COVID-19 vaccines may induce Chilblain-like lesions, similar lesions have been witnessed in mildly infected coronavirus patients as well. The current literature reports numerous cases of COVID-19 infection-associated chilblains [15,71]. In a study by Casas et al [71] involving 375 COVID-19 patients, 19% of cutaneous reactions manifested as CLL. The authors highlighted the occurrence was more prevalent in younger patients [71].

Piccolo V et al [72] in their research noted that feet alone were mostly affected (85.7%) while those having both feet or hands affected together, and hands alone contributed only 7% and 6% respectively. Similar evidence was observed in the study by Recalcati et al [73] whereof 14 described cases, two cases had both extremity involvement, eight had feet while only four had hands involvement.

However, the major concern is many patients reported, was that they had negative PCR results. Research postulates several theories behind it [13]. One of them specified the relatively late CLL lesion appearance in COVID-19, during the convalescent phase, by which the viral products are no longer detectable on PCR [13,74]. Another clue to pathophysiology has been postulated by considering CLL as a cutaneous expression of a type 1 interferon (IFN-1) response. This may lead to viral product clearance before immunoglobulin production, manifesting as failed serological detection [75,76]. An escalated interferon score was observed in 40% of patients in the study by Lesort et al [77]. Hence, we may hypothesize that high IFN response benefitted the patients, reducing viral replication and defining why the patients were asymptomatic.

Conclusions

There are several limitations in the study highlighting which can lead to a specific conclusion in the future. Firstly, the studies included in this review are limited. Studies with larger sample sizes are required to draw associations between chilblain-like lesions and COVID vaccination. Secondly, the treatment regimen reported in the cases differs drastically with no background reasoning for the choices. Thirdly, one of the included study, Nebreda et al did not specify patients age. More importantly, the cases did not report the side effects of the medications, which is crucial in determining the future of the treatment. It also would have highlighted if the patient recovered via medicines or the pernio self-resolved. Lastly, Nebreda et al only provided an overview and did not list any specifications for each case. Although the overall incidence of Chilblains following COVID-19 vaccination is low, there is still a strong need to find out the exact mechanism behind this to redefine the safety and administration criteria of the vaccines and to formulate a proper management protocol. Similarly, there is a need to address the association between these chilblain-like lesions with gender and different demographic settings. There is an overwhelming need to address issues related to vaccines and their hesitancy amongst the population to successfully restore normal life.

References


The Use of Dermoscopy in the Delineation of Basal Cell Carcinoma for Mohs Micrographic Surgery: a Systematic Review With Meta-Analysis

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Key words: Mohs micrographic surgery, Slow Mohs, dermoscopy, dermatoscopy, basal cell carcinoma


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ABSTRACT

Introduction: Several studies investigated the use of dermoscopy in the delineation of basal cell carcinoma (BCC) for Mohs micrographic surgery (MMS) with conflicting results.

Objectives: The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of the use of dermoscopy-guided MMS in the treatment of BCC.

Methods: We included all comparative studies. Cases of BCC treated using dermoscopy-guided MMS (or slow MMS) were compared to those treated with curettage-guided MMS or “standard” MMS.

Results: A total of 6 studies including 508 BCCs were reviewed. There was no statistically significant difference in the proportion of total margin clearance on the first MMS stage between BCCs removed using dermoscopy-guided MMS and those that had curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS.

Conclusions: Dermoscopy allows visualization of structures up to 1mm into the dermis. Therefore, it is rational to use it for lateral margin evaluation. Currently, there are two comparative studies showing the efficacy of dermoscopy for lateral margin evaluation during MMS. Future studies are required to develop an evidence-based recommendation regarding the utility of dermoscopy in MMS.
Introduction

Basal cell carcinoma (BCC) is the most prevalent skin cancer worldwide [1]. The overall incidence has been steadily rising in the last decade throughout the world due to a burgeoning aging population and increased surveillance and diagnosis [2].

The biological behavior of BCC depends on the tumor subtype [1,2]. Undiagnosed and untreated BCC could lead to extensive local destruction and increase both functional and cosmetic morbidity making the treatment and repair approach challenging for the physician.

The National Comprehensive Cancer Network (NCCN) has established guidelines of care for BCCs [3]. High-risk BCCs include recurrent BCC, tumors with ill-defined borders, located on high-risk mask area of the face, arising on sites of prior radiation therapy or harboring aggressive histological features [3]. There are multiple treatment options for BCC such as ablative laser, photodynamic therapy, curettage, cryosurgery, imiquimod, and sonic hedgehog pathway inhibitors [12,2]. However, surgical excision remains the gold standard for treatment of most BCCs [1]. Standard excision is performed with a predefined clinical margin in order to achieve low recurrence rates. Mohs micrographic surgery (MMS) is a specialized surgical technique that combines surgery with pathology. MMS uses horizontal frozen sections to obtain complete margin control resulting in minimal tissue removal with low recurrence rates [1]. MMS proved to be superior to standard excision for high-risk BCC [1]. Slow Mohs is a variant of MMS using formalin-fixed paraffin-embedded sections with similar outcome [4].

Dermoscopy, also known as dermatoscopy or epiluminescence microscopy, is a non-invasive imaging technique widely employed for the diagnosis of skin cancers. Some specific dermoscopic patterns are helpful in the diagnosis of BCC [5]. The use of dermoscopy in the demarcation of surgical margins is another scope of its application. For instance, the use of dermoscopy in MMS might help reduce the number of Mohs stages and achieve surgical margin control within the 1st Mohs stage [4,6-11].

Many studies investigated the effectiveness of dermoscopy in tumor delineation for MMS but with varying outcomes [4,6-11]. While some suggested that dermoscopy could help reduce the number of Mohs stages and therefore shorten operative time and cost [4,9,11], others argued against the usefulness of this approach [6,12]. The ambiguity of these findings is further hampered by the lack of randomized studies and systematic reviews.

Objectives

The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of the use of dermoscopy-guided MMS in the treatment of BCC.

Methods

Search Strategy

This systematic review with meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. We searched the PubMed and Scopus databases from inception up to January 26, 2022 to identify eligible studies. We aimed to identify all relevant studies published in English language. We used the following search algorithm: (“Basal cell carcinoma”) AND (“Mohs surgery” or “Slow Mohs” or “micrographic surgery” or “3-D histology” or “microscopically controlled surgery”) AND (“dermoscopy” or “dermatoscopy” or “epiluminescence microscopy”). The PubMed and Scopus search strategies are available as supplementary material.

Inclusion and Exclusion Criteria of Studies

Two review authors (NL and FH) independently screened titles and abstracts for eligible studies. Eligible articles were identified on the basis of the following inclusion criteria: (i) comparative studies having at least a group of BCCs treated with dermoscopy-guided MMS, (ii) studies that used a control group of BCCs treated with visual inspection and/or curettage-guided MMS, (iii) articles published in English language. For eligible studies, full articles were retrieved in full and analyzed by two independent authors (NL and FH). Any discrepancy between the two investigators was resolved by consensus.

PICO(S): Populations, Interventions, Comparison, Outcome Measures, Types of Studies

We included all comparative observational as well as randomized clinical trials (RCT). Participants with BCC regardless of the clinical and histological subtype of the tumor were eligible for inclusion.

Cases of BCC treated using dermoscopy-guided MMS (or slow MMS) were compared to those treated with curettage-guided MMS or “standard” MMS. The latter uses visual inspection alone to delineate the tumors. All types of dermoscopy techniques were eligible, regardless of the polarization mode (polarized vs. nonpolarized mode) and the device type (hand-held dermoscopy or video dermoscopy).

The main outcome measure was the proportion of total margin clearance on the first MMS stage. The secondary outcome measures included the: (i) number of Mohs stages required to achieve complete margin control, (ii) the lateral margin involvement rate, and (iii) the recurrence rate.

If one or more outcome measures were missing, we contacted the corresponding author at least twice (with at least one-week interval) to ask whether full data were available. If the contact was unsuccessful, the corresponding article was excluded from the analysis.
Assessment of the risk of bias
Two review authors (NL and FH) independently assessed the quality of consistency and the risk of bias in the eligible studies. Any disagreement was resolved by discussion or by consensus with a third author (CD). MINORS score was used for observational studies [14]. RCT were evaluated using the Jadad score [15].

Data Synthesis and Statistical Analysis
Results were reported as Odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data (proportion of total margin clearance on the first MMS stage, lateral margin involvement, and recurrence rates) and standardized mean difference with standard error of the mean for continuous data (number of Mohs stages). A random-effects model was used. Forest plots summarized the data. Funnel plot was used to investigate the existence of publication bias. Strategies for addressing heterogeneity included performing a random-effects meta-analysis and subgroup analyses. We performed all calculations using Comprehensive meta-analysis 3.0 package.

We investigated heterogeneity using Cochran Q test. Evaluation of the percentage of variation between the sample estimates was performed using the Higgins $I^2$ statistic.

Results
Results of the Search
The literature search identified 289 articles (Figure 1). After removing duplicates, 69 articles were screened for eligibility. Fifty-five records were excluded, including not relevant articles (N = 30), papers not published in English (N = 3), editorials and commentary (N = 11), review articles (N = 10) and book chapters (N = 2). Fourteen full-text articles were assessed for eligibility. Among these, 4 were excluded (case reports and noncomparative studies) [16-19]. Three research letters were excluded [11,20,21]. Among these research

Figure 1. Flow diagram.
letters, two compared dermoscopy to naked eye examination in BCC margin evaluation but the number of Mohs stages in each study group expressed in mean with standard deviation was not available [11,20]; and one article included only BCC evaluated using dermoscopy prior to MMS [21]. A randomized open-label study comparing visual inspection, curettage, and dermoscopy in tumor delineation for MMS was excluded because no outcome measure was available for each study group [12]. Contact with the corresponding authors of this study was unsuccessful. Six articles were ultimately included in the present systematic review. Of these, 2 studies were from Asia-Pacific region, 1 from North America, 1 from South America, 1 from Europe, and 1 from Africa (Table 1) [4,6-10].

Description of Included Studies

Of the 6 included studies, 2 were RCTs [6,7], and four were observational studies [4,8-10]. There was no randomized controlled study available for the present systematic review. All included studies were conducted in university-setting centers [4,6-10]. These studies had no funding support and corresponding authors declared no conflicts of interest [4,6-10].

The number of BCCs evaluated ranged from 40 to 197 BCCs per study. The total number of evaluated BCCs was 508. Suzuki et al included both BCC (N = 40) and squamous cell carcinomas (N = 6). The latter were excluded from the analysis. Three studies specified BCC subtypes [6,7,9]. Asilian and Momeni included only nodular BCC [6], and Gurgan and Gatti only infiltrative BCC [7]. Dika et al included various BCC subtypes including nodular (N = 40) and morphoform BCCs (N = 40) [9].

Recurrent BCCs were excluded in three studies [4,6,7]. One study included only recurrent BCC following ablative laser treatment [10]. Two studies enrolled both primary and recurrent BCC (Table 1) [8,9].

Four studies compared 2 interventions for MMS: tumor delineation using naked eye examination versus dermoscopy-guided margin assessment [4,7,8,10]. One of the studies compared dermoscopy-guided MMS to curettage-guided MMS [9]. Asilian and Momeni compared 3 groups: tumor demarcation using naked eye examination (N = 20), dermoscopy (N = 20) and curettage (N = 20) [6].

For the primary outcome “total margin clearance on the first MMS stage”, we assumed that BCCs that underwent more than one Mohs stage showed at least one positive margin. Thereby, the number of BCCs showing total margin clearance on the first MMS stage was extracted from 5 articles [4,7-10].

The secondary outcomes included the mean number of Mohs stages, the recurrence rate, and the number of positive lateral margins after the first Mohs stage. The mean number of Mohs stages in each study group was specified in 5 articles [4,6-9]. However, related standard deviations were only available in 3 articles [4,6,7]. Contact with the corresponding authors of these studies was unsuccessful. Therefore, we did not have the required data to carry out the up-mentioned analysis for these articles [4,6,7].

Only two studies reported the number of positive lateral margins after the first Mohs stage [4,10]. Relapse rates were described in 2 articles [4,9], ranging between no relapse and 4%, after a follow-up period of 10 ± 5 and more than 62.5 months respectively.

Assessment of Risk of Bias in Included Studies

For RCT [6,7], the Jadad scale was 1 and 2. Overall, the methodological quality was poor. There was no disagreement between the review authors (NL and FH) about the studies quality.

For non-randomized studies [4,8-10], the MINORS index ranged between 14 and 16.

Effects of Interventions

When comparing dermoscopy-guided vs. standard MMS for BCC treatment, there was no statistically significant difference in the proportion of total margin clearance on the first MMS stage (OR 0.86, 95% CI 0.41 to 1.15; five studies [4,7-10]) (Figure 2).

There was no statistically significant difference in the number of Mohs stages when comparing dermoscopy-guided and standard MMS (The standardized mean difference -0.17, 95% CI -0.51 to 0.17; three studies [4,6,7]) (Figure 3). For this outcome measure, we found heterogeneity (Tau2 = 0.220 et I2 = 57.334%). Subgroup analysis was performed based on the technique used for Mohs surgery (frozen sections versus formalin-fixed paraffin-embedded sections). After subgroup analysis, including studies using MMS [6,7], there was no heterogeneity (Tau2 = 0.000), the pooled standard difference in means showed no statistically significant difference. Only one study reported the number of Mohs stages in patients treated using Slow Mohs [4]. Since iterative Mohs sessions rely on histopathological examination of excised tissue, it is possible that the type of tissue processing technique (frozen sections in MMS vs formalin-fixed paraffin-embedded sections in slow Mohs) is responsible for heterogeneity regarding the outcome measure (number of Mohs stages).

A significantly lower proportion of positive lateral margins was obtained with dermoscopy-guided MMS compared with standard MMS based on visual inspection (OR 0.16, 95% CI 0.06 to 0.83; 2 studies [4,10]) (Figure 4). With regards to recurrence rates, available data was insufficient for meta-analysis. Two studies reported the number of recurrences after MMS [4-9]. One of these
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study objective</th>
<th>Study design</th>
<th>Coverage period</th>
<th>Intervention groups</th>
<th>BCC subtypes in each group</th>
<th>Recurrent BCC before Mohs surgery</th>
<th>Cases included in the meta-analysis</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asilian and Momeni [6]</td>
<td>2012</td>
<td>Iran</td>
<td>To compare three ways (naked eye examination, dermoscopy, and curettage) for determining tumor extension before initiation of MMS,</td>
<td>RCT</td>
<td>2011-2012</td>
<td>3 groups: tumor demarcation using naked eye examination (N = 20), dermoscopy (N = 20) and curettage (N = 20)</td>
<td>nodular BCC in all included cases</td>
<td>not included in the study</td>
<td>ND</td>
<td>40</td>
</tr>
<tr>
<td>Gurgen and Gatti [7]</td>
<td>2012</td>
<td>United States</td>
<td>To compare the final number of MMS stages performed using dermoscopy and visual inspection of infiltrative basal cell carcinoma</td>
<td>RCT</td>
<td>ND</td>
<td>2 groups: - dermoscopy group (N = 20) - visual inspection group (N = 20)</td>
<td>infiltrative BCC in all cases</td>
<td>not included in the study</td>
<td>ND</td>
<td>40</td>
</tr>
<tr>
<td>Suzuki et al [8]</td>
<td>2014</td>
<td>Brazil</td>
<td>To assess the impact of dermoscopy on the demarcation of surgical margins for MMS and ascertain whether the use of this method can shorten operative time</td>
<td>observational study</td>
<td>2009-2011</td>
<td>2 groups: - Group1: Mohs surgery (N = 21) - Group 2: Mohs surgery with dermoscopy-guided margins (N = 23)</td>
<td>ND</td>
<td>Group 1: 3/21 Group 2: 4/23</td>
<td>44</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Table 1 continues*
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study objective</th>
<th>Study design</th>
<th>Coverage period</th>
<th>Intervention groups</th>
<th>BCC subtypes in each group</th>
<th>Recurrent BCC before Mohs surgery</th>
<th>Cases included in the meta-analysis</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dika et al [9]</td>
<td>2017</td>
<td>Italy</td>
<td>to evaluate the role of videodermoscopy and curettage in MS for a better margin evaluation intraoperatively</td>
<td>observational study</td>
<td>2005-2010</td>
<td>2 groups:</td>
<td>Group 1: - nodular BCCs (N = 21) - pigmented BCCs (N = 28) - morpheiform BCCs (N = 20) Group 2: - nodular BCCs (N = 19) - pigmented BCCs (N = 28) - morpheiform BCCs (N = 20)</td>
<td>Group 1 (31/102) Group 2 (26/95)</td>
<td>197</td>
<td>Group 1 (82.6) Group 2 (62.5)</td>
</tr>
<tr>
<td>Shin et al [10]</td>
<td>2020</td>
<td>Korea</td>
<td>To evaluate the usefulness of dermoscopy in determining MMS surgical margins of BCCs with a history of ablative laser treatment.</td>
<td>observational study</td>
<td>2009-2016</td>
<td>2 groups:</td>
<td>ND</td>
<td>All cases were recurrent BCC (previously treated by ablative laser). Recurrent cases after radiotherapy or surgical resection were excluded.</td>
<td>133</td>
<td>ND</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Study objective</td>
<td>Study design</td>
<td>Coverage period</td>
<td>Intervention groups</td>
<td>BCC subtypes in each group</td>
<td>Recurrent BCC before Mohs surgery</td>
<td>Cases included in the meta-analysis</td>
<td>Follow-up (months)</td>
</tr>
<tr>
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</tbody>
</table>

**BCC = basal cell carcinoma; ND = not described; RCT = randomized clinical trial.**
Figure 2. Comparison of the proportion of positive margins after the first Mohs stage using dermoscopy-guided vs. standard or curettage-guided MMS for BCC treatment

<table>
<thead>
<tr>
<th>STUDY NAME</th>
<th>STATISTICS FOR EACH STUDY</th>
<th>ODDS RATIO AND 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ODDS RATIO</td>
<td>LOWER LIMIT</td>
</tr>
<tr>
<td>GURGEN AND GATTI, 2012</td>
<td>1,238</td>
<td>0,343</td>
</tr>
<tr>
<td>SUZUKI ET AL., 2014</td>
<td>1,222</td>
<td>0,372</td>
</tr>
<tr>
<td>DIKA ET AL., 2017</td>
<td>0,521</td>
<td>0,295</td>
</tr>
<tr>
<td>SHIN ET AL, 2020</td>
<td>0,958</td>
<td>0,463</td>
</tr>
<tr>
<td>LITAIE M ET AL, 2020</td>
<td>0,247</td>
<td>0,079</td>
</tr>
<tr>
<td></td>
<td>0,686</td>
<td>0,409</td>
</tr>
</tbody>
</table>

Three studies excluded recurrent BCC [4,6,7], while one study included only recurrent BCC following ablative laser [10]. Of the included studies, pooling of the data was feasible for 3 evaluated outcomes. There was no statistically significant difference in the proportion of total margin clearance on the first MMS stage between BCCs removed using dermoscopy-guided MMS and those that had curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS.

To the best of our knowledge, no systematic review addressed the question of whether dermoscopy is useful for delineating BCC margins for MMS. Que published a comprehensive narrative review on noninvasive imaging technologies used for the delineation of BCC in the setting of

Conclusions

In the present study, we aimed to assess the effectiveness of dermoscopy as an ancillary tool for MMS. Six studies were included: 2 RCTs [6,7], and 4 observational studies [4,8-10]. The total number of evaluated BCCs was 508. Three studies specified the subtypes of evaluated BCCs [6,7,9]. Studies reported a recurrence rate of 3% in BCCs treated with dermoscopy-guided MMS and of 5.2% in those treated with curettage-guided MMS (P = 0.48; Fisher exact test) after a follow-up period of 82.6 and 62.5 months respectively [9]. In the second study, both study groups showed no recurrence after a mean follow-up period of 10 ± 5 months [4].
META ANALYSIS (OUTCOME: NUMBER OF MOHS SESSIONS)  

(Q TEST) P = 0.034 - $I^2$: 70.3%

Figure 3. Comparison of the number of Mohs stages using dermoscopy-guided vs. standard or curettage MMS for BCC treatment

META ANALYSIS (OUTCOME: POSITIVE LATERAL MARGINS AFTER THE FIRST MOHS SESSIONS)  

(Q TEST) P = 0.550 - $I^2$: 0%

Figure 4. Comparison of the proportion of positive lateral margins after the first Mohs stage using dermoscopy-guided vs. standard or curettage guided MMS for BCC treatment
MMS [22]. Three technologies were discussed: dermoscopy, confocal microscopy, and optical coherence tomography. Only the number of Mohs stages was evaluated as an outcome measure in relation to dermoscopy. Que stated that dermoscopy did not prove to decrease the number of Mohs stages. In our systematic review, there was no statistically significant difference in the number of Mohs stages between the use of dermoscopy or visual inspection for MMS (the standardized mean difference -0.17, 95% CI -0.51 to 0.17; three studies [4,6,7]). A hypothesis to explain this finding is that dermoscopy utility is limited to the first Mohs stage. Subsequent stages would only rely on the surgeon’s skills and experience.

In the present systematic review, there was no significant association between the use of dermoscopy and the proportion of total margin clearance on the first MMS stage. Surgical margin assessment includes both deep and lateral margin evaluation. A dermoscope is a magnifying instrument that enables visualization of pigmented structures and vessels up to 1mm into the dermis and therefore would not allow for deep margin evaluation [5]. Hence, it is rational to use it for lateral margin evaluation [4,10].

There are several potential implications for both practice and research. Relapsing BCCs and BCCs bearing aggressive histopathological features may exhibit a subclinical extension of their lateral margins [23]. This could result in recurrences and incomplete surgical excision [23]. Further studies assessing lateral margin involvement are needed. In addition, future research is warranted to investigate the utility of dermoscopy for tumor delineation in high-risk BCC.

Combining two imaging techniques is beyond the scope of the present systematic review. Recently, Lupu et al evaluated whether BCC lateral excision margins could be precisely evaluated preoperatively through the use of dermoscopy and reflectance confocal microscopy [23]. In this study, 18 patients (20 BCCs, mostly nodular: 12/20) were included. The authors concluded that dermoscopy served as an accurate guide during reflectance confocal microscopy [23]. The global accuracy of the procedure was 93.1% (95% CI 0.77–0.99) [23].

The present systematic review sought to summarize the existing data on the possible use of dermoscopy for tumor delineation in MMS. However, certain limitations apply to the results depicted herein. First, our sample size was limited by the scarcity of research on this subject in the literature. Only two included studies evaluated the use of dermoscopy for lateral margin assessment. Therefore, these results should be interpreted with caution. Second, some studies had missing data on outcome measures and hence were excluded from the data analysis. Third, the histopathological subtype of BCC, which can act as a confounding factor, was not indicated in all included studies. This may hinder the interpretation of findings and undermine their accuracy. Finally, both dermoscopy and MMS are operator-dependent procedures [4]. Thus, controlled, consistent and reproducible results are not readily attainable.

Despite these limitations, this systematic review is a comprehensive summary on the reported use of dermoscopy for BCC delineation in MMS to date. Overall, our data suggest that dermoscopy could improve lateral margin assessment within the first Mohs stage. Future randomized clinical trials are required to develop an evidence-based recommendation regarding the utility of dermoscopy in MMS.

References


Eruptive Non-melanoma Skin Cancers/Squamous Atypia Following Skin Surgery. Report of Two New Cases, Concise Review of the Literature With Special Emphasis on Treatment Options

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4 Skin Cancer Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy

Key words: Eruptive non-melanoma skin cancers, keratoacanthomas after cutaneous surgery, keratoacanthomas AND split-thickness skin graft, cutaneous squamous cell carcinomas AND split-thickness skin graft


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ABSTRACT

Introduction: Eruptive cutaneous squamous cell carcinomas (ESCC), eruptive squamous atypia (ESA) and eruptive keratoacanthomas (EKA) are different terms used to describe the occurrence of multiple cutaneous squamous neoplasms after skin surgery, laser treatment, traumas, such as tattoos, and local or systemic medical treatments.

ESCC have been reported to arise at the sites of skin surgery, including the area affected by the primary tumor and split thickness skin graft (STSG) donor and recipient sites.

Objectives: The aim of this study is to report 2 additional cases of ESCC after skin surgery and make a critical revision of the literature, analyzing the clinical, histological features and outcomes of ESCC after cutaneous surgery.

Methods: Up to August 2021, according to our systematic review of the literature, we have collected 19 published articles and a total of 34 patients, including our 2 cases.

Results: The results of this review highlight five red flags that clinicians should consider: (i) lower and upper limbs represent the cutaneous site with the highest risk, representing 83,78% of the cases in the...
Introduction

Eruptive cutaneous squamous cell carcinomas (ESCC), eruptive squamous atypia (ESA) and eruptive keratoacanthomas (EKA) are different terms used to describe the occurrence of multiple cutaneous squamous neoplasms occurring after skin surgery, laser treatment, traumas, such as tattoos, local or systemic medical therapies. In this paper, we decided to use only the term ESCC.

ESCC have been reported to arise at the sites of skin surgery, including the area affected by the primary tumor and split thickness skin graft (STSG) donor and recipient sites [1-19]. The best therapeutic option for ESCC after surgery in our opinion is still a challenge.

Objectives

The aim of our study is to report 2 additional cases of ESCC after skin surgery and make a critical revision of the literature, analyzing the clinical, histological features and outcomes of ESCC after cutaneous surgery [18]. An overview of this rarely reported condition is provided, in order to raise awareness of this clinical entity and of the treatment options.

Methods

We identified studies indexed in PubMed from its inception to June 31, 2021. All papers reported in the present study involved human clinical studies, including case reports, case series and reviews. Search parameters included the terms “Keratoacanthomas after cutaneous surgery”, “Keratoacanthomas AND STSG”, “Cutaneous squamous cell carcinomas AND STSG”, “Cutaneous squamous cell carcinomas after cutaneous surgery”, “squamous cell carcinoma after Mohs Micrographic surgery (MMS)”, “eruptive squamous cell carcinoma and surgery”, “eruptive squamous atypia and surgery”, “eruptive keratoacanthomas and surgery”, “koebnerized cutaneous squamous cell carcinoma”.

A subsequent review of the relative bibliographies aimed to identify any undetected reports. We collected sex, age, involved cutaneous area, surgical procedure, medical treatment and histopathology findings of primary cutaneous squamous cell carcinomas of all the patients included in this review. Furthermore, we reported the time lapse from the primary surgery to the onset of ESCC, clinical and histological features, management, recurrences and outcome. In addition, we describe here our personal experience with two patients visited at the Skin Cancer Unit of Bologna between January 2012 and August 2021, who developed ESCC after cutaneous squamous cell carcinoma (CSCC) excision and reconstruction with STSG.

Results

Up to August 2021, according to our systematic review of the literature, we found only 19 published articles (Table 1).

A total of 34 ascertained patients, including our two cases, were included in this study, with a sex ratio F/M = 0.88, a mean age = 68.94 years (standard deviation [SD] = 13.6).

The main clinical features of the 34 patients diagnosed with ESCC after surgery are reported in Table 2.

The extremities (upper and lower limbs) were the sites most frequently involved by primary tumors, representing 83.78% of cases in our sample. The second most involved site was the head, with 13.51% of cases. Regarding our two patients, the first had a CSCC of the head and the second a cutaneous SCC of the right leg.

Histological examination of the primary skin cancer was consistent with a CSSC in 30/37 cases (81.08%), while basal cell carcinoma, actinic keratosis, malignant melanoma and lentigo maligna were detected in 7 cases (18.92%).

Different surgical techniques were used for the excision of the primary skin tumors, although classic fusiform excision, excision plus STSG, MMS and subsequent reconstruction with or without STSG were the most commonly performed procedures, in 32/37 cases (86.49%).

The main clinical features of the ESCC after skin surgery are reported in Table 3. The median time to the onset is approximately 6 weeks, and in 28/34 of the patients (82.35%) it occurred within 16 weeks from the primary surgery.

Surprisingly, ESCC occurred in the area of the skin affected by the primary tumor in 26/37 of the cases literature; (ii) the median time to onset of ESCC is approximately 6 weeks; (iii) primary cutaneous squamous cell carcinomas were completely excised with free margins on histologic examination in the totality of the cases of the literature, and therefore ESCC should not be considered recurrences; (iv) any surgical technique involves a risk to promote ESCC; (v) treatment of ESCC includes medical treatment, surgery or combined surgical and medical treatment.

Conclusions

This review highlights 5 red flags which could support clinicians in the diagnosis and management of ESCC after skin surgery.
<table>
<thead>
<tr>
<th>Study and Year</th>
<th>N.</th>
<th>Case</th>
<th>Age, Sex</th>
<th>Area involved</th>
<th>Surgery procedure performed</th>
<th>Medical Treatment</th>
<th>Histopathology findings</th>
<th>Time Onset after Surgery (Weeks)</th>
<th>Area involved</th>
<th>Histopathology findings</th>
<th>Surgical Treatment</th>
<th>Medical Treatment</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neilson et al, 1988</td>
<td>1</td>
<td>59, M</td>
<td>dorsum of his right ring finger (upper limbs)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>SCCs</td>
<td>12</td>
<td>GDS</td>
<td>SCC</td>
<td>Ex</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Clark et al., 2015</td>
<td>1</td>
<td>73, F</td>
<td>B Legs (lower limb)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>SCCs</td>
<td>4</td>
<td>ExS + GDS</td>
<td>KASP</td>
<td>Ex + STSG</td>
<td>Acitretin 25 mg/d</td>
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<td></td>
</tr>
<tr>
<td>Juhász and Marmur, 2014</td>
<td>1</td>
<td>82, F</td>
<td>R Shin (lower limb)</td>
<td>MMS + STSG</td>
<td>3 months of topical mupirocin + warm 2% milk compresses for loss of the graft, wound dehiscence, and persistent ulceration</td>
<td>KA</td>
<td>20</td>
<td>MMS site</td>
<td>KA</td>
<td>MMS</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Bangash et al, 2009</td>
<td>5</td>
<td>81, F</td>
<td>L Wrist and Hand (upper limb)</td>
<td>MMS</td>
<td>None</td>
<td>SCC</td>
<td>4</td>
<td>MMS site</td>
<td>SCC</td>
<td>MMS</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>63, M</td>
<td>L Hand (upper limb)</td>
<td>MMS</td>
<td>None</td>
<td>SCC</td>
<td>8</td>
<td>MMS site</td>
<td>SCC</td>
<td>MMS</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>54, M</td>
<td>L occipital Ridge (head)</td>
<td>Ex</td>
<td>None</td>
<td>SCC</td>
<td>7</td>
<td>ExS</td>
<td>SCC with features of KA</td>
<td>MMS</td>
<td>None</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>58, M</td>
<td>Left leg and R Elbow (upper and lower limb)</td>
<td>MMS</td>
<td>None</td>
<td>SCC; SCC</td>
<td>6</td>
<td>MMS site; MMS site</td>
<td>SCC; SCC</td>
<td>MMS</td>
<td>None</td>
<td>Yes, Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>55, F</td>
<td>L Hand (upper limb)</td>
<td>MMS + STSG</td>
<td>None</td>
<td>SCC</td>
<td>72</td>
<td>MMS site</td>
<td>SCC</td>
<td>MMS + STSG</td>
<td>Acitretin 10 mg/d</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 continues
Table 1. Eruptive non-melanoma skin cancers following skin surgery: literature review and our cases. (continued)

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>N.</th>
<th>Patients</th>
<th>First Skin Lesion</th>
<th>Eruptive NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hadley et al, 2009</td>
<td>3</td>
<td>1</td>
<td>67, M</td>
<td>Forearm (upper limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>70, F</td>
<td>Forearm (upper limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>88, F</td>
<td>B Legs (lower limb)</td>
</tr>
<tr>
<td>Haik et al, 2008</td>
<td>1</td>
<td>64, M</td>
<td>Left Big Toe (lower limb)</td>
<td>A + STSG</td>
</tr>
<tr>
<td>Goldberg et al, 2004</td>
<td>6</td>
<td>1</td>
<td>72, M</td>
<td>L Leg and Finger (lower limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>69, M</td>
<td>L Forearm, (upper limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>74, F</td>
<td>R Leg (lower limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>79, M</td>
<td>R Forearm (upper limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>71, M</td>
<td>R Thigh (lower limb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>75, M</td>
<td>R Forehead (head)</td>
</tr>
<tr>
<td>Hussain et al, 2010</td>
<td>1</td>
<td>52, M</td>
<td>R Hand (upper limb)</td>
<td>Ex + STSG</td>
</tr>
<tr>
<td>Study and Year</td>
<td>Patients First Skin Lesion Eruptive NMSC</td>
<td>Time Onset after Surgery (Weeks)</td>
<td>Area involved</td>
<td>Histopathology findings</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------</td>
<td>-------------------------------</td>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Ponnuvelu et al, 2011</td>
<td>2 (58, M)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>nodulocystic BCC</td>
</tr>
<tr>
<td></td>
<td>2 (88, F)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>KA</td>
</tr>
<tr>
<td>Lee et al, 2017</td>
<td>1 (95, F)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>KA</td>
</tr>
<tr>
<td>Saltivig and Matzen, 2018</td>
<td>1 (78, F)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>MM</td>
</tr>
<tr>
<td>Kimyai-Asadi et al, 2004</td>
<td>1 (76, M)</td>
<td>Ex</td>
<td>None</td>
<td>SCC</td>
</tr>
<tr>
<td>Negase et al, 2016</td>
<td>1 (78, F)</td>
<td>FTSG</td>
<td>None</td>
<td>AK</td>
</tr>
<tr>
<td>Marcus and Brady, 2021</td>
<td>1 (39, F)</td>
<td>MMS + STSG</td>
<td>None</td>
<td>SCC</td>
</tr>
<tr>
<td>Vergara et al, 2007</td>
<td>1 (80, F)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>KA</td>
</tr>
<tr>
<td>L. Kearney et al, 2015</td>
<td>1 (48, M)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>MM</td>
</tr>
<tr>
<td>Morritt and Khandwala, 2012</td>
<td>1 (82, F)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>SCCs</td>
</tr>
<tr>
<td>Gambichler 2021</td>
<td>2</td>
<td>49 F</td>
<td>Leg (lower limb)</td>
<td>MMS + STSG</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>60 M</td>
<td>Back of the hand (upper limb)</td>
<td>MMS + STSG</td>
</tr>
</tbody>
</table>

*Table 1 continues*
### Table 1. Eruptive non-melanoma skin cancers following skin surgery: literature review and our cases. (continued)

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>N.</th>
<th>Case</th>
<th>Age, Sex</th>
<th>Area involved</th>
<th>Surgery procedure performed</th>
<th>Medical Treatment</th>
<th>Histopathology findings</th>
<th>Time Onset after Surgery (Wks)</th>
<th>Area involved</th>
<th>Histopathology findings</th>
<th>Surgical Treatment</th>
<th>Medical Treatment</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Que et al 2019</td>
<td>1</td>
<td>62M</td>
<td>R and L legs (Lower limbs)</td>
<td>Ex</td>
<td>None</td>
<td>3 SCC</td>
<td>Not specified</td>
<td>Exs sites</td>
<td>Suspected eruptive squamous atypia</td>
<td>None</td>
<td>Intralesional 5-fluorouracil plus acitretin</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Chessa et al, 2021</td>
<td>2</td>
<td>1</td>
<td>65M</td>
<td>R occipital area of the scalp (head)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>SCC</td>
<td>4</td>
<td>STSG primary excision site</td>
<td>SCC</td>
<td>Ex</td>
<td>Acitretin 25 mg/die</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>80F</td>
<td>R Leg (lower limb)</td>
<td>Ex + STSG</td>
<td>None</td>
<td>SCC</td>
<td>6</td>
<td>STSG primary excision site</td>
<td>SCC</td>
<td>Ex</td>
<td>acitretin 25 mg/daily and intralesional methotrexate 10 mg/weekly</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AK = Actinic Keratosis; A = Amputation; B = Bilateral; CEMP = Cutaneous extramedullary plasmacytomas; Co = Courretage; ED = Electrodesiccation; Ex = Excision; ExS = Excision Site; F = Female; FTSG = Full-Thickness Skin Graft; GDS = Graft Donor Site; KA = Keratoacanthoma; KASP = Keratoacanthomatous atypical squamous proliferation; L= Left; N/A= data not available; LM = Lentigo Maligna; M = Male; MM = Malignant Melanoma; MMS = Mohs Micrographic Surgery; MU = Marjolin Ulcer; N = Number of patients involved; SCC = Squamous Cell Carcinoma; SG = Skin Graft; SGS = Skin Graft Site; Sh = Shave; STSG = Split-Thickness Skin Graft; R = Right; SBCC = Superficial Basal Cell Carcinoma;
Table 2. Clinical findings of primary tumor in 34 patients diagnosed with eruptive squamous cell carcinomas/squamous atypia following skin surgery.

<table>
<thead>
<tr>
<th>Findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of primary skin cancers excised</td>
<td>37</td>
</tr>
<tr>
<td>Patients with one primary skin cancer</td>
<td>32 (94.12%)</td>
</tr>
<tr>
<td>Patients with two primary skin cancer</td>
<td>2 (5.88%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (52.94%)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (47.06%)</td>
</tr>
<tr>
<td>Mean Age ± SD</td>
<td>68.94± 13.06 (39-95)</td>
</tr>
<tr>
<td>Cutaneous site involved</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>5 (13.51%)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>12 (32.43%)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>19 (51.35%)</td>
</tr>
<tr>
<td>Chest</td>
<td>1 (2.70%)</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
</tr>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>25 (67.56%)</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>5 (13.51%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3 (8.12%)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2 (5.41%)</td>
</tr>
<tr>
<td>Actinic Keratosis</td>
<td>1 (2.70%)</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>1 (2.70%)</td>
</tr>
<tr>
<td>Treatment performed</td>
<td></td>
</tr>
<tr>
<td>Excision</td>
<td>6 (16.22%)</td>
</tr>
<tr>
<td>Excision plus Split-Thickness Skin Graft</td>
<td>12 (32.43%)</td>
</tr>
<tr>
<td>Mohs Micrographic Surgery</td>
<td>10 (27.03%)</td>
</tr>
<tr>
<td>Mohs Micrographic Surgery plus Split-Thickness Skin Graft</td>
<td>5 (13.51%)</td>
</tr>
<tr>
<td>Coupettage plus electrodesiccation</td>
<td>2 (5.41%)</td>
</tr>
<tr>
<td>Amputation plus Split-Thickness Skin Graft</td>
<td>1 (2.70%)</td>
</tr>
<tr>
<td>Excision plus Full-Thickness Skin Graft</td>
<td>1 (2.70%)</td>
</tr>
</tbody>
</table>

Table 3. Main features of eruptive squamous cell carcinomas/squamous atypia following skin surgery.

<table>
<thead>
<tr>
<th>Features</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of primary skin cancers excised</td>
<td>37</td>
</tr>
<tr>
<td>Patients with one primary skin cancer</td>
<td>32 (94.12%)</td>
</tr>
<tr>
<td>Patients with two primary skin cancers</td>
<td>2 (5.88%)</td>
</tr>
<tr>
<td>Time onset after surgery median weeks</td>
<td>6 (2-960)</td>
</tr>
<tr>
<td>Cutaneous site involved by eruptive squamous cell carcinomas/squamous atypia</td>
<td></td>
</tr>
<tr>
<td>Cutaneous site affected by primary tumor treated with Mohs micrographic surgery</td>
<td>14 (37.84%)</td>
</tr>
<tr>
<td>Cutaneous site affected by primary tumor treated with simple excision</td>
<td>6 (16.22%)</td>
</tr>
<tr>
<td>Cutaneous site affected by primary tumor treated with split-thickness skin graft</td>
<td>4 (10.81%)</td>
</tr>
<tr>
<td>Cutaneous site affected by primary tumor treated with coupettage plus electrodesiccation</td>
<td>2 (5.41%)</td>
</tr>
<tr>
<td>Graft donor site</td>
<td>8 (21.61%)</td>
</tr>
<tr>
<td>Cutaneous site affected by primary tumor treated with excision and graft donor site</td>
<td>3 (8.11%)</td>
</tr>
<tr>
<td>Cutaneous site affected by eruptive squamous cell carcinomas/squamous atypia</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>3 (8.11%)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>10 (27.03%)</td>
</tr>
</tbody>
</table>
(70.27%), the graft donor site (GDS) or both. All primary tumors in our series were completely excised, with free margins on histological examination. In our sample, cutaneous STSG was harvested from the lateral thigh in almost all patients and was therefore considered the only cutaneous donor site affected.

ESCC were histologically represented by CSCC and keratoacanthomas (KA) in 91.9% of cases while in 3 patients was not performed histopathological examination. The same histological diagnosis between the primary skin cancer and the ESCC was found in 50% of cases and eruptive KAs or CSCCs also appeared after excision of lentigo maligna or melanoma.

The surgical treatment of ESCC is extremely varied (Table 3). However, simple fusiform excision and MMS were the most used surgical techniques, comprising 62.16% of cases. Medical therapy was associated with surgery in 7/34 cases while two patients were treated with isotretinoin 40 mg/die without surgery and 1 patient was treated with intraläsional 5-fluorouracil plus acitretin 20 mg daily (Table 3).

<table>
<thead>
<tr>
<th>Features</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limbs</td>
<td>11 (37.84%)</td>
</tr>
<tr>
<td>Donor site affected by eruptive squamous cell carcinomas/squamous atypia</td>
<td>13 (35.14%)</td>
</tr>
<tr>
<td>Histopathology of eruptive squamous cell carcinomas/squamous atypia</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>18 (48.65%)</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>14 (37.84%)</td>
</tr>
<tr>
<td>Marjolin Ulcer</td>
<td>1 (2.70%)</td>
</tr>
<tr>
<td>Keratoacanthomatous atypical squamous proliferation</td>
<td>1 (2.70%)</td>
</tr>
<tr>
<td>Not performed histopathological examination</td>
<td>3 (8.11%)</td>
</tr>
<tr>
<td>Concordance between histological diagnosis of primary tumor and and eruptive squamous cell carcinomas/squamous atypia</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>17 (50.00%)</td>
</tr>
<tr>
<td>no</td>
<td>17 (50.00%)</td>
</tr>
<tr>
<td>Treatment performed</td>
<td></td>
</tr>
<tr>
<td>Surgery without medical treatment</td>
<td></td>
</tr>
<tr>
<td>Excision</td>
<td>13 (38.24%)</td>
</tr>
<tr>
<td>Excision plus flap</td>
<td>2 (5.88%)</td>
</tr>
<tr>
<td>Mohs Micrographic Surgery</td>
<td>10 (29.42%)</td>
</tr>
<tr>
<td>Curettage plus electrodesiccation</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Surgery associated with medical treatment</td>
<td></td>
</tr>
<tr>
<td>Excision plus acitretin 25 mg/die</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Excision plus acitretin 25 mg/daily and intraläsional methotrexate 10 mg/weekly</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Excision plus split-thickness skin graft and acitretin 25 mg/die</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Mohs micrographic surgery plus split-thickness skin graft and acitretin 25 mg/die</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Mohs micrographic surgery plus isotretinin 40 mg/die</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Curettage plus electrodesiccation plus imiquimod cream application</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Curettage plus electrodesiccation isotretinin 40 mg/die</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Medical treatment without surgery</td>
<td></td>
</tr>
<tr>
<td>Isotretinin 40 mg/die without surgery</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Intraläsional 5-fluorouracil plus acitretin</td>
<td>1 (2.94%)</td>
</tr>
<tr>
<td>Recurrences</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (40.54%)</td>
</tr>
<tr>
<td>No</td>
<td>17 (45.95%)</td>
</tr>
<tr>
<td>Not available</td>
<td>5 (13.51%)</td>
</tr>
</tbody>
</table>
Of note, the paper from Que et al describe 30 cases of ESCC, but only one case is clearly and without doubts associated to a previous skin surgery and was added to our review [19].

The treatment was effective without recurrences in 17/37 cases; these patients were treated with surgery alone in 13 cases, combined surgical and medical treatment in 2 cases and with medical therapy in two cases. Isotretinoin 40 mg/die resulted effective alone and in combination with Mohs surgery [7]. Surgery combined with acitretin (25 mg/daily) plus intralesional methotrexate 10 mg/weekly was administered to the first our patient, favoring a complete resolution without recurrences (Figure 1).

Recurrences of ESCC were reported in 15/37 cases (10 treated with surgery alone and 5 treated with combined medical and surgical therapy). All 15 cases with recurrences were treated with a combination of surgery and medical therapy. Patients showed a complete resolution of ESCC recurrences at follow-up in 6/15 cases (40%). The following therapies proved effective on recurrences: 1 to 2 mL in intralesional administration of 50 mg/mL 5-fluorouracil (FU) [5,19]; acitretin (25 mg/day); combined intralesional 5-FU and methotrexate to reduce the toxicity of any single agent [5]; isotretinoin 40 mg/die [7]; oral acitretin (20 to 25 mg/day) [10,15]; lastly our second patient was treated with surgery plus 25 mg/daily acitretin (Figure 2). In 5/34 cases data on recurrences were not available in the papers (Table 1).

Finally, 2/34 patients died, due to lung cancer in one case and CSSC metastases in 1 of our patients, who was also affected by chronic lymphatic leukemia [5].

Conclusions

The pathogenesis of ESCC is not clarified and is currently a matter of debate [18-23].

Local appearance of ESCC could be referred to residual cancer tissue following the excision of the primary tumor [21,22]. However, eruptive NMSC in skin graft donor sites have no local relation to the original tumor site, even if tumor cells could theoretically spread by direct contact (if the same needle was used to infiltrate the tumor and donor site) or systemically (via the blood or lymphatic vessels). Moreover, ESCC different from primary tumor excised, such as KAs after lentigo maligna or melanoma, have been reported [6,7,11,16].

The patient immune system must also be taken into account. Immunodeficiency induced by drugs or other diseases, such as hematologic disorders, may explain the propensity for the development of cancer, inducing a generalized ‘field of cancerization’ that can induce a Koebner phenomenon and the development of new cutaneous cancers in the site of surgery [17,21-23].

The presence of a chronic lymphatic leukemia may have been a predisposing factor in one of our patients for the development of ESCC soon after surgery, as well as a negative prognostic factor for the development of distant metastases, leading to exitus. Interestingly, the only patient that developed distant metastases after the development of ESCC had the primary CSSC located on the scalp, while none of the cases of ESCC reported in the Literature localized both on upper or lower extremities had a poor prognosis. This distinction can be important and to confirm this statement in the paper of Que et al reporting 30 cases of eruptive squamous atypia, without the specification if the onset was spontaneous, after surgery or other treatments o traumas, all the
patients had a localization on upper or lower extremities or both and none developed metastases [19].

According to Nwabudike LC et al, ESCC could also be a perfect example of locus minoris resistentiae as described by Ruocco [20,24]. An immunocompromised district can be defined as a regional destabilization of the neuro-immuno-cutaneous system, and surgical procedures, as well as the scars resulting from them, impair both lymph circulation and neuro-immune crosstalk in the traumatized area [24,25]. Gambichler and colleagues demonstrated in two patients affected by “koebnerized” CSCC that the wound healing processes can induce a proliferative stimulus and growth factors release, which could be able to promote the growth of pre-neoplastic keratinocytes and cancer formation, on the basis of pre-existing altered epigenetic pathways and cell cycle dysregulation [18].

The results of this review highlight five red flags that clinicians should consider in the diagnosis and management of ESCC after skin surgery. First of all, the extremities (lower and upper limbs) represent the cutaneous site with the highest risk, representing 82.35% of the cases in the literature.

The second point concerns the time of onset of ESCC, which is wide, ranging from 2 to 960 weeks. The median time to onset of ESCC is approximately 6 weeks, and in 28/34 (82.35%) of cases reported in the literature they appeared within 16 weeks from the primary cutaneous surgery.

The third point is that primary CSCC were completely excised with free margins on histologic examination in all cases of the literature, and therefore the ESCC reported were not considered recurrences. This concept has important legal implications.

The fourth point is that any surgical technique, including classic fusiform excision, excision plus STSG, MMS and subsequent reconstruction with or without STSG, involves a risk to promote ESCC, which can surprisingly affect both the area affected by the primary tumor and the graft donor site.
Large longitudinal surgery studies are necessary to evaluate the risk assessment of surgical technique and ESCC.

The fifth point is that the treatment of ESCC includes medical treatments, surgery or combined surgical and medical treatments. Que et al reported a 67% resolution rate using intralesional 5-fluorouracil for eruptive squamous atypia of the upper and lower limbs. However, 5-fluorouracil is chemotherapeutic agent that can be used only in hospital, it is off-label and much more difficult to obtain in Italy than intralesional methotrexate or oral acitretin. Moreover, Que et al have specified that it can be used only for lesions smaller than 15 mm, while over 15 mm of diameter, surgery is still considered the best choice. According to our review, ESCC recurrences are a medical challenge and have been treated combining surgical and medical treatment, with complete recurrences are a medical challenge and have been treated combining surgical and medical treatment, with complete resolution in about one third of patients [5,7,10,15]. When using a nonsurgical treatment modality for ESCC, the concern of missing an aggressive CSSC is an important issue, that must be kept in mind, especially in sites different from the upper and lower extremities.

In conclusion, even though the pathogenesis remains unclear, this review highlights 5 red flags which could help support clinicians in the diagnosis and management of ESCC after skin surgery.

References


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Pigmented Macules on the Head and Neck: A Systematic Review of Dermoscopy Features

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Key words: dermoscopy, lentigo maligna melanoma, solar lentigo, pigmented actinic keratosis, head and neck


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ABSTRACT

Introduction: Differentiating early melanoma from other flat pigmented lesions on the head and neck is challenging both clinically and dermoscopically, partly due to the wide differential diagnosis and the lack of specific diagnostic algorithms.

Objectives: To review publications covering the dermoscopic features of pigmented macules on the head and neck.

Methods: Embase and PubMed (Medline) database from January 2015 to January 2021 were searched using a four-step search. Keywords used were dermoscopy/dermatoscopy or epiluminescence microscopy, lentigo maligna, lentigo maligna melanoma, lichen-planus-like-keratosis, solar lentigo, seborrheic keratosis, pigmented actinic keratosis (PAK), pigmented Bowen disease (pBD), pigmented intraepidermal carcinoma (pIEC) and head and neck.

Results: The commonest reported dermoscopic features of facial melanoma were irregular dots, atypical dots/globules, asymmetric pigmented follicular openings, rhomboid gray/black structures, increased vascular network, brown globules/dots and a pattern of circles. Pseudopods, radial streaming, blue white veil, irregular blotches, scar-like depigmentation and atypical pigment network were recorded in low frequencies. For PAK, pBD and pIEC perifollicular erythema, white/yellow surface scale, linear wavy vessels around hair follicles, hair follicular openings surrounded by a white halo, evident follicles or follicular or keratotic plugs, rosette sign and sharply demarcated borders were the salient features.

Conclusions: Further studies are needed to determine the dermoscopic criteria for pigmented melanocytic and non-melanocytic lesions on the head and neck. Furthermore, there is a gap in the knowledge of site-specific dermoscopic features on specific sites, namely ears, nose, cheeks, scalp and neck which will also benefit from further studies.
Introduction

Melanoma diagnosis on chronic sun-damaged skin is challenging to clinicians both clinically and dermoscopically [1-5]. This is partly due to the overlap of melanoma features with non-melanoma skin lesions including solar lentigo (SL) (Figure 2), seborrhoeic keratosis (SK) (Figure 3), pigmented actinic keratosis (PAK)/ pigmented Bowen disease (pBD)/ pigmented intraepidermal carcinoma (pIEC) (Figures 4 and 6) and lichen planus like keratosis (Figure 1).
Compared to other parts of the body, the head and neck region has features of sun-damage, increased elastosis, increased intensity of hair follicular openings and skin appendages as well as flat rete ridges creating a pseudo-pigment network. These collectively can render the extra-facial diagnostic algorithms for melanoma diagnosis unreliable. Furthermore, prior therapeutic interventions like cryosurgery, curettage/electrodestruction as well as topical treatment may result in scarring and hypopigmentation adding to the diagnostic difficulty.

Approximately 20% of melanomas occur on the head and neck [7]. The estimated five year survival rate on the head and neck is lower (74%) compared to melanoma located on the extremities (84%) and trunk (82%) [8,9].

Figure 2. Left side – Macroscopy: a 75-year-old male (BH) with a pigmented lesion on the left side of the nose. Right side - Dermoscopy - showing gray areas (arrows), white circles (square) and brown interfollicular pigmentation (oval shape). Diagnosis: pigmented actinic keratosis and solar lentigo, combined. Fotofinder dermoscopy, Medicam 1000, magnification x20.

Figure 3. Left side – Macroscopy - A 71-year-old male with a pigmented lesion on the left side of the forehead. Right side – Dermoscopy - pink and gray areas (oval shapes), ill-defined margins, increased vascularity with curved vessels (square). Diagnosis: seborrheic keratosis. Fotofinder dermoscopy, Medicam 1000, magnification x20.
Figure 5. Macroscopy - Left side - A 71-year-old male with a pigmented lesion on the left side of the forehead with peppering or annular granular structures composed of scattered dots of gray pigmentation all over the lesion. Dermoscopy - Right side - Diagnosis: lichen planus like keratosis. Fotofinder dermoscopy, Medicam 1000, magnification x20.

Figure 4. (A) Macroscopy - A 50-year-old female with a lesion on the left cheek. (B) Dermoscopy - Diagnosis: pigmented actinic keratosis. (C) Macroscopy - A 67-year-old male with a pigmented lesion on the right eyebrow. (D) Dermoscopy - Diagnosis: pigmented Bowen disease. (E) Macroscopy - A 33-year-old female with a left cheek lesion. (F) Dermoscopy - Diagnosis: pigmented intraepidermal carcinoma. Fotofinder dermoscopy, Medicam 1000, magnification x20.
In the second step studies covering melanoma, LM, LMM, LPLK, solar lentigo (SL), SK, pigmented actinic keratosis (PAK), pBD, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were identified. Studies conducted on the head and neck were included in the third search step. The last step was combining the above three steps.

This review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. To identify all relevant studies the reference section of the studies was searched for studies not identified by the search. Where possible, some authors were contacted. Studies on raised lesions and those studies based exclusively on reflectance confocal microscopy (RCM) were excluded. Other exclusion criteria were studies based on surgical or medical treatments as well as studies based on conjunctiva and other mucosal surfaces. Finally, abstract only and non-English studies were also excluded.

PubMed and Embase search were conducted as detailed below:

PubMed (Medline)

Dermoscopy
“dermoscopy”[MeSH Terms] OR dermoscopy[tiab] OR dermatoscopy[tiab]

Pigmented lesions

Head/neck

Embase

Dermoscopy
‘epiluminescence microscopy/exp OR dermoscopy:ti,ab OR dermatoscopy:ti,ab

Lentigo maligna (LM), formerly known as Hutchinson melanotic freckle (HMF) is the commonest type of in situ melanoma on sun-exposed areas [10]. It tends to develop clinically as a brown macule on chronic sun-exposed sites. Dermoscopically the differential diagnosis is variable and the clinical and dermoscopic margins tend to be ill-defined which can lead to incomplete excisions [11]. Progression to an invasive stage is called lentigo maligna melanoma (LMM) which represents 4%-15% of all invasive melanomas [12]. Estimations of lifetime risk of LM progressing into LMM is 5%-20% [11].

Dermoscopy is a non-invasive technique that increases the diagnostic accuracy of skin lesions. In expert hands diagnostic accuracy for melanoma can be increased by up to 49% [13,14]. Histology is considered to be the gold standard for diagnosis. Additional stains including melan-A/MART-1 stain was found to aid in the detection of invasive disease in 29% of melanoma cases [15]. Histologically LM is characterized by atypical melanocytes proliferating along the dermo-epidermal junction as single cells or nests. Pagetoid spread may be minimal or absent. In contrast, LMM displays atypical melanocytes in single cells and nests within the dermis [16]. The diagnosis of LM and LMM can be challenging due to the extent of ultraviolet damage and/or prior therapeutic intervention like cryosurgery or topical treatments [11]. The dermoscopic features also vary with the site of the melanoma, histological type and depth of invasion (Table 1) [9].

## Objectives

To review publications covering the dermoscopic features of pigmented macules on the head and neck.

## Methods

Embase and PubMed (Medline) database from January 2015 to January 2021 were searched. A 4-step systematic review was conducted. The first step used keywords including dermoscopy/dermatoscopy or epiluminescence microscopy.

In the second step studies covering melanoma, LM, LMM, LPLK, solar lentigo (SL), SK, pigmented actinic keratosis (PAK), pBD, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) were identified. Studies conducted on the head and neck were included in the third search step. The last step was combining the above three steps.

This review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. To identify all relevant studies the reference section of the studies was searched for studies not identified by the search. Where possible, some authors were contacted. Studies on raised lesions and those studies based exclusively on reflectance confocal microscopy (RCM) were excluded. Other exclusion criteria were studies based on surgical or medical treatments as well as studies based on conjunctiva and other mucosal surfaces. Finally, abstract only and non-English studies were also excluded.

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Pigmented lesions

Head/neck

Embase

Dermoscopy
‘epiluminescence microscopy/exp OR dermoscopy:ti,ab OR dermatoscopy:ti,ab

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**Table 1. Cengiz et al 2015. Dermoscopic Features according to the histological subtype of melanoma on the head and neck.**

<table>
<thead>
<tr>
<th>Dermoscopic Features</th>
<th>LMM</th>
<th>LMM- in situ</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetry</td>
<td>24  (60%) (κ = 1)</td>
<td>12  (60%) (κ = 0.65)</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Pseudo-network</td>
<td>24  (60%) (κ = 0.80)</td>
<td>8  (40%) (κ = 0.70)</td>
<td>P = 0.0005</td>
</tr>
<tr>
<td>Irregular dots</td>
<td>32  (80%) (κ = 0.83)</td>
<td>15  (75%) (κ = 1)</td>
<td>P = 0.121</td>
</tr>
<tr>
<td>Scar-like depigmentation</td>
<td>12 (30%) (κ = 0.86)</td>
<td>6  (30%) (κ = 0.69)</td>
<td>P = 0.032</td>
</tr>
<tr>
<td>2 different colors</td>
<td>32  (80%) (κ =1)</td>
<td>15  (75%) (κ = 0.83)</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>3 different colors</td>
<td>8  (20%) (κ =1)</td>
<td>5  (25%) (κ = 0.80)</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>4 different colors</td>
<td>–</td>
<td>–</td>
<td>P = 0.0005</td>
</tr>
</tbody>
</table>
Clinical and Dermoscopic Features of LM and LMM on the Head and Neck

The following extra-facial dermoscopy features: pseudo-pods, radial streaming, blue white veil, irregular blotches, scar-like depigmentation and atypical pigment network were recorded in low frequencies, (Table 2) [9]. In some studies the criteria of extra-facial LMM were found in only 52.4% of cases [17]. The typical clinical presentation is commonly a flat pigmented macule resembling other differentials including PAK/pBD/pIEC, LPLK, SL and SK [14,15].

The common reported dermoscopic features of facial melanoma were (Figure 1):

- Two or less colors and
- Asymmetric pigmented follicular openings (APFO) or folliculotropism,
- Brown colored globules and dots,
- Signet-ring like structures,
- A pattern of circles.
- Increased density of vascular network,
- Red rhomboid structures,
- Irregular dots (granularity or peppering),
- Atypical dots and globules (gray, slate gray or blue),
- Rhomboid gray/black structures,

In some studies multiple irregular gray/blue dots, referred to as “granularity” or “peppering”, were found in 93.5% of extra-facial melanoma, 26.5% of extra-facial benign lesions

<table>
<thead>
<tr>
<th>Table 2. Cengiz et al 2015. Frequency of analyzed criteria in head and neck melanomas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermoscopic Characteristics</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Asymmetry in two axes</td>
</tr>
<tr>
<td>Atypical dots</td>
</tr>
<tr>
<td>Radial streaming</td>
</tr>
<tr>
<td>Pseudopods</td>
</tr>
<tr>
<td>Blue-white veil</td>
</tr>
<tr>
<td>Mixed vascular pattern</td>
</tr>
<tr>
<td>Scar-like depigmentation</td>
</tr>
<tr>
<td>Rhomboidal Structures</td>
</tr>
<tr>
<td>Atypical pigment network</td>
</tr>
<tr>
<td>Pseudo-network</td>
</tr>
<tr>
<td>Asymmetric pigmented follicular openings</td>
</tr>
<tr>
<td>Annular-granular pattern</td>
</tr>
<tr>
<td>Colors (3 or more)</td>
</tr>
<tr>
<td>Blotches</td>
</tr>
<tr>
<td>Increased density of vascular network</td>
</tr>
<tr>
<td>Red rhomboid structures</td>
</tr>
<tr>
<td>Abrupt demarcation</td>
</tr>
</tbody>
</table>
accuracy of 0.72 for the diagnosis of LM seven criteria were found significant [21]. These criteria were:

• Asymmetric pigmented follicular openings,
• Rhomboid structures,
• Target-like pattern,
• Perifollicular gray color,
• Dark blotches,
• Moth eaten borders and
• Fingerprint-like structures.

In an attempt to differentiate between LM and PAK a “newly developed algorithm” claimed a diagnostic accuracy of 86.5%, sensitivity of diagnosis of LM versus PAK of 82.7%, specificity of 92.0%, positive predictive value (PPV) of 93.8% and negative predictive value (NPV) of 78.4%. The eight statistically significant dermoscopic features for differentiation of LM from PAK were [4]:

• Light brown color,
• A structureless zone, varying in color from brown/tan to black,
• In focus discontinuous brown lines,
• Brown-to-gray incomplete circles,
• A brown or black structureless zone obscuring hair follicles,
• A brown (tan) eccentric structureless zone,
• A blue structureless zone and scales.

The features found to contribute the most to a diagnosis of LM were:

• Structureless zones ranging from brown/tan to black,
• Blue structureless zones,
• Brown to black structureless zones obscuring hair follicles and
• Incomplete brown to gray circles.

On the other hand the features suggestive of PAK were (Figure 4):

• The occurrence of light structureless zones,
• Brown (tan) eccentric scales and
• In focus brown discontinuous lines.

Clinical and dermoscopic features of PAK, pBD and pIEC

The main reported dermoscopic features of PAK, pBD and pIEC (Figure 4) were:

• Perifollicular erythema or red pseudo-network,
• White to yellow surface scale,
• Linear wavy vessels around hair follicles,
• Hair follicular openings surrounded by white halo,
• Evident follicles or follicular or keratotic plugs,
• Rosette sign (four dot clods, when polarized light dermoscopy is used) and
• Sharply demarcated borders.

In non-pigmented facial actinic keratosis (AK) four dermoscopic features were recorded [22], notably (Figure 4):

• Erythema surrounding the hair follicles or red pseudo-network (95%),
• White to yellow surface scale (85%),
• Linear wavy vessels around hair follicles (81%) and
• Hair follicle openings filled with yellow keratotic plugs (66%) and/or surrounded by white halo (100%).

These features collectively gave a picture of a “strawberry pattern”, (Figures 4 and 6).

Actinic keratoses tend to present as multiple macules on the same patient suggesting a “signature” pattern [22]. In lighter skin Fitzpatrick types these are usually non-pigmented AK while on darker skins they are pigmented [23]. Another clue to PAK on head and neck were “evident follicles” which were “visible follicles without pigmentation” and “projected as the dominant dermatoscopic feature” [2]. “Non-pigmented follicles associated with either interfollicular pigment, interfollicular erythema or both” was considered a strong dermoscopic clue to pIEC shared with PAK in the head and neck [24]. That description corresponded to the evident follicles described [2]. These dermoscopic findings were significantly positive for actinic keratosis in other studies [24], in addition to the rosette sign (also called four dot clods, seen with polarized light dermoscopy), large irregular linear vessels surrounding hair follicles and peripheral pigmentation [25]. Serpentine vessels were present in almost half of the cases of pIEC head and neck compared to coiled vessels in pIEC elsewhere [24]. A combination of red pseudo-network, hair follicular opening surrounded by a white halo and follicular plugs has been predicted to have a sensitivity of 90.7%, specificity of 81.82%, PPV of 90.70% and a NPV of 81.82% (Figure 6) [25].

For PAK/pBD scales show a PPV of 72.2% (specificity of 94.2%), white circles a PPV of 68.8% (specificity of 94.2%) and sharply demarcated borders a PPV of 44.2% (specificity of 86.0%), (Figure 6 and Table 3) [1]. The absence of scales in pigmented macules on the head and neck in combination with multiple colours with brown being present in all cases, as well pink, white and gray dominated in pigmented intraepidermal carcinoma (pIEC) in that location as per Inskip et al compared to Cameron et al [6,24]. In some studies, PAK/pBDs/pIEC had incomplete circles reported in 73.1% of cases compared to 71.3% for melanoma, nil reported circle in circle or double circles, nil reported gray structures, rhomboid structures in 94.7% compared to 91.7% in melanoma, nil dotted, serpentine or branched vessels, nil ulcerations and 86.0% well demarcated margins, (Table 3 and Figure 6) [1].

Figure 6. Macroscopy - Left side - A 43-year-old male with a pink, slightly scaly lesion located on the left temple. Dermoscopy - Right side - Dermoscopy features include a ‘strawberry’ appearance, with white-to-yellow follicular keratotic plugs (ellipse) surrounded by a whitish halo, and background erythema/red pseudo-network. In addition, 4-dot-structures (circles) are seen in some parts of the lesion, which when coalescing they form white complete circles (arrow). In parts of the lesion white lines are seen which are different from hairs (squares)-Fotofinder dermoscopy, Medicam 1000, magnification x20. Diagnosis: actinic keratosis.
Table 3. Tschandl et al 2015. Diagnostic indices of dermatoscopic clues to flat malignant facial lesions. Numbers in braces depict 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>RR (relative risk)</th>
<th>PPV (positive predictive value)</th>
<th>NPV (negative predictive value)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Any gray structure</td>
<td>8.9 (1.2–64.7)</td>
<td>13.3% (8.6–19.3)</td>
<td>98.5% (91.9–99.8)</td>
<td>95.8% (78.8–99.3)</td>
<td>30.6% (24.5–37.2)</td>
</tr>
<tr>
<td>Vessels as dots</td>
<td>3.5 (1.1–11.8)</td>
<td>33.3% (5.3–77.3)</td>
<td>90.6% (86.1–94.0)</td>
<td>8.3% (1.3–27.0)</td>
<td>98.1% (95.3–99.5)</td>
</tr>
<tr>
<td>Incomplete circles</td>
<td>3.0 (1.4–6.5)</td>
<td>18.4% (10.5–29.0)</td>
<td>93.9% (89.1–97.0)</td>
<td>58.3% (36.7–77.9)</td>
<td>71.3% (64.8–77.2)</td>
</tr>
<tr>
<td>Gray circles</td>
<td>4.6 (2.2–9.7)</td>
<td>26.5% (15.0–41.1)</td>
<td>94.2% (89.9–97.1)</td>
<td>54.2% (32.8–74.4)</td>
<td>83.3% (77.7–88.0)</td>
</tr>
<tr>
<td>Rhomboids</td>
<td>2.0 (0.7–5.3)</td>
<td>18.2% (5.3–40.3)</td>
<td>90.8% (86.2–94.3)</td>
<td>16.7% (4.8–37.4)</td>
<td>91.7% (87.2–95.0)</td>
</tr>
<tr>
<td>Circle in a circle</td>
<td>2.0 (0.3–12.3)</td>
<td>20.0% (3.3–71.2)</td>
<td>90.2% (85.7–93.7)</td>
<td>4.2% (0.7–21.2)</td>
<td>98.1% (95.3–99.5)</td>
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<tr>
<td><strong>Basal cell carcinoma</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any gray structure</td>
<td>7.7 (1.1–56.6)</td>
<td>11.6% (7.2–17.3)</td>
<td>98.5% (91.9–99.8)</td>
<td>95.2% (76.1–99.2)</td>
<td>30.1% (24.1–36.7)</td>
</tr>
<tr>
<td>Branched vessels</td>
<td>17.8 10.5–30.3</td>
<td>100.0% (62.9–100.0)</td>
<td>94.4% (90.6–97.0)</td>
<td>38.1% (18.1–61.6)</td>
<td>100.0% (98.3–100.0)</td>
</tr>
<tr>
<td>Serpentine vessels</td>
<td>12.2 (6.7–22.1)</td>
<td>83.3% (36.1–97.2)</td>
<td>93.2% (89.1–96.0)</td>
<td>23.8% (8.3–47.2)</td>
<td>99.5% (97.5–99.9)</td>
</tr>
<tr>
<td>Ulceration</td>
<td>11.7 (6.0–22.7)</td>
<td>66.7% (33.0–89.9)</td>
<td>94.3% (90.5–96.9)</td>
<td>38.1% (18.2–61.6)</td>
<td>98.2% (95.4–99.5)</td>
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<tr>
<td><strong>Pigmented actinic keratosis/Bowen disease</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White circles</td>
<td>3.0 (2.2–4.3)</td>
<td>68.8% (50.0–83.9)</td>
<td>77.4% (71.1–82.9)</td>
<td>31.9% (21.2–44.2)</td>
<td>94.2% (89.5–97.2)</td>
</tr>
<tr>
<td>Sharply demarcated border</td>
<td>1.7 (1.2–2.6)</td>
<td>44.2% (29.1–60.1)</td>
<td>74.6% (68.0–80.5)</td>
<td>27.5% (17.5–39.6)</td>
<td>86.0% (79.8–90.8)</td>
</tr>
<tr>
<td>Incomplete circles</td>
<td>1.7 (1.1–2.5)</td>
<td>39.5% (28.5–51.4)</td>
<td>76.2% (69.0–82.5)</td>
<td>43.5% (31.6–56.0)</td>
<td>73.1% (65.8–79.6)</td>
</tr>
<tr>
<td>Rhomboids</td>
<td>2.3 (1.5–3.5)</td>
<td>59.1 (36.4–79.3)</td>
<td>74.3% (68.0–80.0)</td>
<td>18.8% (10.4–30.1)</td>
<td>94.7% (90.2–97.6)</td>
</tr>
<tr>
<td>Four-dot clod</td>
<td>2.1 (1.0–4.5)</td>
<td>60.0% (15.4–93.5)</td>
<td>71.9% (65.7–77.6)</td>
<td>4.3% (1.0–12.2)</td>
<td>98.8% (95.8–99.8)</td>
</tr>
<tr>
<td>Scale</td>
<td>3.4 (2.5–4.8)</td>
<td>72.2% (54.8–85.8)</td>
<td>78.9% (72.7–84.3)</td>
<td>37.7% (26.3–50.2)</td>
<td>94.2% (89.5–97.2)</td>
</tr>
</tbody>
</table>

Conclusions

The accurate diagnosis of LM and LMM is paramount for their early appropriate management. The differential diagnosis is variable. Different studies have compared different dermoscopic features of LM, LMM, PAK, pBD and pIEC. Not all features were compared similarly. Some studies documented sensitivity and specificity while other publications listed the percentage of lesions showing the feature. Some compared positive predictive value (PPV) and negative predictive value (NPV) of the dermoscopy features. To date the used terminology is not unified in spite of some frequently used terms. Further studies are needed to agree on the criteria specific to each diagnosis, namely LM, LMM, PAK, pBD and pIEC. Furthermore, according to the current literature, there is a gap in the knowledge of site-specific dermoscopic features on the head and neck. These site-specific areas include the ears, nose, cheeks, scalp and neck. The development of specific algorithms based on deep learning models (eg integrated scoring classifiers) could be of great help in differentiating LM/LMM of the head and neck from their simulators in clinical practice [26]. This would benefit from further studies.

References


Apremilast in Psoriasis Patients With Serious Comorbidities: a Case Series and Systematic Review of Literature

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ABSTRACT

Introduction: Patients with serious comorbidities are traditionally excluded from clinical trials. Apremilast is not contraindicated in active infections, malignancy and serious hepatic or renal impairment, but real-life data is needed to support this recommendation.

Objectives: The aim of this paper is to present our personal as well as literature-sourced real-world evidenced on apremilast use in psoriasis patients with serious baseline comorbidities.

Methods: A case-series and systematic literature review were performed. The psoriasis archives of a tertiary-care hospital, four electronic databases (MEDLINE, ScienceDirect, Cochrane Library, Google scholar) and other sources were searched (January 2014 – July 2021). Identified records were considered eligible, if they reported on the use of apremilast monotherapy in psoriasis patients with chronic infections, history of malignancy, serious liver, renal, psychiatric, or other disease(s).

Results: At least 841 psoriasis patients with serious baseline diseases received apremilast. Only 3 cases of cancer progression and no infection reactivations or worsening of other diseases were documented. No increased frequency/severity of adverse events or reduced drug efficacy were noted. Main limitations of this study are the exclusion of a few reports due to inappropriately documented data and the fact that at least some patients might have been counted more than once.

Conclusions: Apremilast is a safe and adequately efficacious option for psoriasis that cannot be treated/is challenging to treat with classic systemic agents and/or biologics.
Introduction

Psoriasis is a chronic cutaneous disease of inflammatory nature, with a worldwide prevalence ranging between 1-3%; it has a substantial negative effect on patient physical well-being and quality-of-life, as well as on national health expenditure [1–3]. Apremilast (Otezla®, Amgen), a small molecular inhibitor of phosphodiesterase 4 (PDE4), has been used for the treatment of psoriatic arthritis and psoriasis since 2014 (first US Food and Drug Administration [FDA] approval). Contrary to biologics, it does not target any one specific component of the inflammatory process involved in the pathophysiology of psoriasis, but rather achieves some sort of equilibrium of pro-inflammatory and anti-inflammatory agents [4,5].

Apremilast comes with a set of favorable attributes, among which are the oral distribution, lower cost comparing to biologics and good safety profile [3,6]. It is not contraindicated in patients with active infections or serious liver impairment, nor is routine lab monitoring necessary. Similarly, it can be administered to patients with past or current malignancy [8]. Patients with severe renal impairment can still receive a reduced dose of apremilast [9]. A pooled analysis (≥ 156 weeks) from the 2 apremilast-approving (ESTEEM) trials showed that serious infection rate was low among patients receiving apremilast, while no serious opportunistic infections or cases of tuberculosis reactivation were noted [10]. However, as patients with chronic infections, cancers and serious co-existing diseases are traditionally excluded from clinical trials testing new drugs, conclusions regarding the use of said drugs in these occasions cannot always be safely drawn [7,11].

Objectives

The purpose of this study is to present our five-year experience in administering apremilast to psoriasis patients with serious comorbidities in the setting of a tertiary-care center in terms of drug safety and efficacy, as well as to concisely portray relevant real-life evidence sourced through a systematic literature search.

Methods

Case Series

The March 2016 (apremilast approval in Greece) to June 30th, 2021 archives of both the Psoriasis Outpatient Clinic and Afternoon Private Clinics of the First Dermatology Department, Aristotle University, Thessaloniki, Greece were consecutively searched for all psoriasis patients having received at least one dose of apremilast. Patients with an appropriately documented chronic/latent infection, recent (past 10 years) malignancy excluding basal cell carcinoma, serious kidney (stage IV and V) or liver (Child-Pugh C) disease, severe psychiatric disorder or other serious illness as was defined by Kelley [12] were included in the study. The following data were retrieved by two collaborating authors (AT and NS): age, gender, comorbidity(-ies), year of comorbidity diagnosis, apremilast dose, baseline Psoriasis Area and Severity Index (PASI), treatment outcome in terms of efficacy, duration of apremilast treatment (weeks) and adverse events (AEs) including adverse outcomes related to comorbidity(-ies) in question. Written informed consent was obtained by all participants. This project was designed and conducted based on the declaration of Helsinki and was approved by the Ethics Committee of the Hospital of Venereal and Cutaneous Diseases, Thessaloniki, Greece.

Systematic Review

Eligibility Criteria

We conducted this systematic review as stated by Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statement. Published and unpublished prospective or retrospective observational studies reporting on the use of apremilast for the treatment of psoriasis patients with serious baseline comorbidities (chronic/latent infections such as tuberculosis, hepatitis and HIV, cancer diagnosis within past ten years excluding basal cell carcinoma, stage IV and V chronic kidney disease hemodialysis, Child-Pugh class C liver disease, serious psychiatric disorders or other serious illness as was defined by Kelley [12]) were considered eligible for inclusion in our study. Clinical trials or studies not presenting real-life data, as well as studies reporting on combination therapy of apremilast and other systemic agents aside from phototherapy, systemic corticosteroids or other medication administered systemically for existing comorbidities were excluded from our review. Only studies performed after 2014 (apremilast first FDA approval) were considered. No language restrictions were placed.

Information Sources

Three electronic databases were searched (MEDLINE, ScienceDirect, and the Cochrane Library electronic databases). Google scholar (https://scholar.google.com/) was also browsed. Abstract compendia of the World Congresses of Dermatology, World Psoriasis and Psoriatic Arthritis Congresses, American Academy of Dermatology Annual Meetings and European Academy of Dermatology and Venereology Annual Congresses of the last five years were examined (online browsing). Last search date for all above mentioned platforms was July 4th, 2021. Amgen® was
contacted and kindly asked to supply our team with any published or unpublished data abiding by our search criteria. The “Reference” section of studies included in our review was hand searched for additional eligible work.

Search Strategy
The following search strategy was used for MEDLINE database and modified accordingly for the rest of searched platforms: (apremilast[Title]) AND (psoriasis[Title/Abstract]) filtered by year of publication (2014 to 2021). The search was performed independently by two authors (AT and NS).

Selection Process and Data Collection
Duplicate records were independently manually removed by two reviewers (NS and AT). Subsequently, two reviewers (AT and NS) independently screened titles and abstracts for relevance to the study objective. The full text of remaining records was read, and eligible studies were included in the review. AT and NS separately extracted the following data from included studies according to a pre-formulated sheet: first author, year of publication / research completion, comorbidity(-ies), age and gender of patient(-s), apremilast dose, baseline PASI, AEs including comorbidity-related events. Any disagreements were resolved in consultation with a third author (ES).

Quality Assessment
Two authors (AT and ES) independently assessed included reports based on two different tools, namely the Joanna Briggs Institute (JBI) critical appraisal tool for case reports/case series and the JBI critical appraisal tool for analytical cross-sectional studies, each comprising eight questions (Supplement). Each study was assigned an overall rating of poor, good or fair, if 0-5, 6-7 or 8 criteria were met respectively.

Results
The psoriasis-archives search returned 16 eligible cases, one of which was not included in the analysis due to incompletely documented patient data (Table 1). No progression of malignancy, reactivation of chronic / latent infection or deterioration of already deficient renal or hepatic function were noted. Apremilast was generally well-tolerated and only mild transient AEs were reported in 6 patients. Patient compliance to treatment was high (three cases of temporary drug discontinuation, < 14 days, due to Covid-19-related restrictions and consequent difficulties in drug prescription). Desired response (PASI50) was not achieved in 1 case and apremilast was therefore discontinued (primary drug failure).

The systematic literature search yielded 52 studies eligible for inclusion (Figure 1). One additional study was identified after the last search date (published July 8th 2021) and does not appear in the flow diagram (Figure 1) [13]. A total of at least 826 psoriasis patients with serious comorbidities (various malignancies – at least 456 patients –, latent / past tuberculosis – 49 patients –, hepatitis B, C and HIV infections – at least 83 patients –, serious renal – 7 patients – or liver impairment – at least 110 patients –, serious psychiatric disorders – 49 patients – or other serious illness as was defined by Kelley [12]) were prescribed apremilast twice or once daily (Table 2). The exact number of patients with serious comorbidities prescribed apremilast was not reported in a few studies, therefore, the numbers mentioned above are a conservative underestimation of the studied population. Included patients manifested all types of psoriasis and/or nail psoriasis. Overall, apremilast was hardly ever associated with negative comorbidity-related outcomes and reported AEs were apparently not more severe or frequent than those experienced by the average psoriasis patient. Sufficient response of psoriasis to apremilast was recorded in most cases. Overall, the quality of included studies was good (Table 3).

Conclusions
This case series and systematic review reports on the use of apremilast in 841 psoriasis patients with serious baseline comorbidities, which would have made the use of classic systemic agents and/or biologics inappropriate or challenging. According to our study, the use of apremilast in this group of patients apparently neither leads to deterioration / exacerbation of severe pre-existing comorbidity(-ies) nor is it associated with an increased risk of adverse events. What is more, drug efficacy does not seem to be affected by the underlying comorbidity, with cases of remarkable response even in erythrodermic patients with very serious underlying diseases. A drug safety profile, especially in the context of pre-existing comorbidities, is one of its major attributes to be taken into consideration, when deciding on a treatment regimen [14]. Psoriasis patients receiving apremilast, as opposed to other systemic agents, seem to have a lower infection risk [15]. Rates of herpes zoster infection were lowest for users of apremilast among a cohort of psoriasis patients treated with biologics and/or small molecules (5.4, 95% CI 1.7-12.6) [16]. Comparing to methotrexate (MTX), as investigated in a cohort of 2845 psoriasis patients treated
viral load, discussion with an infectious-disease specialist is warranted, with apremilast and acitretin being the preferred options [19]. Based on the same recommendations, the preferred options for short-term systemic treatment of psoriasis patients with chronic hepatitis C infection are adalimumab and etanercept, as there is not enough evidence to support the use of other biologics and apremilast [19]. As far as chronic hepatitis B infection is concerned, ustekinumab, apremilast, cyclosporine and acitretin are preferred [19]. Apremilast has shown potential in the treatment of psoriasis patients with a history of malignancy. It may even help treat lung cancer, as PDE4 is expressed in lung cancer cells [20].

In the current pandemic era, it is important to examine a drug safety with regards to the COVID-19 infection. According to the World Health Organization, psoriasis patients on with nine systemic agents in Spain, apremilast had a lower infection (incidence rate 0.3 [95% CI 0.1-0.9]) and malignant neoplasm risk (incidence rate 0.1 [95% CI 0-0.7]) [14].

Psoriasis may be more severe or difficult to treat in patients with HIV infection [17,18]. What is more, HIV-positive patients are immuno-compromised and prone to reactivation of latent infections [17]. According to the 2020 Belgian practical recommendations for the treatment of psoriasis in HIV-positive patients, apremilast and acitretin are considered first-line choices [17]. Furthermore, many biologics (adalimumab, certolizumab pegol, etanercept, infliximab, ustekinumab, guselkumab, risankizumab, brodalumab, secukinumab, ixekizumab) can be used in patients receiving highly active antiretroviral therapy (HAART) and having undetectable viral load [19]. In case of detectable viral load, discussion with an infectious-disease specialist is warranted, with apremilast and acitretin being the preferred options [19]. Based on the same recommendations, the preferred options for short-term systemic treatment of psoriasis patients with chronic hepatitis C infection are adalimumab and etanercept, as there is not enough evidence to support the use of other biologics and apremilast [19]. Apremilast has shown potential in the treatment of psoriasis patients with a history of malignancy. It may even help treat lung cancer, as PDE4 is expressed in lung cancer cells [20].

In the current pandemic era, it is important to examine a drug safety with regards to the COVID-19 infection. According to the World Health Organization, psoriasis patients on
Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram detailing the number and origin of records identified, included in and excluded from this systematic review, as well as the reasons for exclusion.
<table>
<thead>
<tr>
<th>Report</th>
<th>Comorbidity</th>
<th>Age/Sex</th>
<th>APR dose</th>
<th>Bas PASI</th>
<th>Tx outcome</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mugheddu 2020 [22]</td>
<td>Recurrent brain oligodendroglioma under temozolomide and prednisone</td>
<td>45/M</td>
<td>30 mg bid</td>
<td>12</td>
<td>Improvement</td>
<td>PASI90 W24; None, stable CD4+ count</td>
</tr>
<tr>
<td>Manfreda 2019 [15]</td>
<td>HIV positive (CD4+ &gt;1000 cells/mm³)</td>
<td>41/M</td>
<td>30 mg bid</td>
<td>10.2</td>
<td>73% PASI</td>
<td>reduction M7; None, stable CD4+ count</td>
</tr>
<tr>
<td>Zarboh1 2019 [5]</td>
<td>HIV positive (CD4+ &gt;1000 cells/mm³)</td>
<td>45/M</td>
<td>30 mg bid</td>
<td>14.7</td>
<td>PASI100 W6</td>
<td>None, cancer course not affected by APR</td>
</tr>
<tr>
<td>Shah 2019 [18]</td>
<td>HIV positive (CD4+ 742/μl)</td>
<td>35/M</td>
<td>30 mg bid</td>
<td>8</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Reddy 2019 [17]</td>
<td>HIV positive (CD4+ &gt;742/μl)</td>
<td>50/M</td>
<td>30 mg bid</td>
<td>10%</td>
<td>None</td>
<td>No changes in the course of comorbidities</td>
</tr>
<tr>
<td>Fotiadou 2018 [33]</td>
<td>Chronic hepatitis B, undetectable viral load</td>
<td>52/F</td>
<td>30 mg bid</td>
<td>13.2</td>
<td>PASI90 W24</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Reddy 2019 [17]</td>
<td>HIV positive (CD4+ &gt;460 cells/mm³)</td>
<td>55/M</td>
<td>30 mg bid</td>
<td>52/F</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Ferriero 2018 [34]</td>
<td>Chronic hepatitis B, decompensated cirrhosis, metastic HCC</td>
<td>50/M</td>
<td>30 mg bid</td>
<td>52/F</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Jeon 2017 [34]</td>
<td>Malignancy: 3, liver disease: 1, alcoholic liver disease: 1, demyelinating disease: 1</td>
<td>60/F</td>
<td>30 mg bid</td>
<td>30 mg bid</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Gottlieb 2021 [36]</td>
<td>Malignancy: 92, serious infection: 52, sleep disorder: 1</td>
<td>60, M</td>
<td>30 mg bid</td>
<td>30 mg bid</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Kahn 2019 [37]</td>
<td>1. renal cell carcinoma</td>
<td>30, F</td>
<td>30 mg bid</td>
<td>30 mg bid</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Nagata 2019 [38]</td>
<td>Chronic myeloid leukemia under imatinib, latent tuberculosis, alcoholism, steatohepatitis</td>
<td>38/F</td>
<td>30 mg bid</td>
<td>30 mg bid</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Vico-Alonso 2020 [40]</td>
<td>Malignancy: 13 (breast, bladder, colorectal), severe infection: 6</td>
<td>38, M</td>
<td>30 mg bid</td>
<td>30 mg bid</td>
<td>PASI75 M6</td>
<td>None, normal Hbload and LFTs</td>
</tr>
<tr>
<td>Perrone 2017 [42]</td>
<td>Malignancy: 13 (breast, bladder, colorectal), severe infection: 6</td>
<td>71, M</td>
<td>30 mg bid</td>
<td>30 mg bid</td>
<td>None, normal Hbload and LFTs</td>
<td></td>
</tr>
<tr>
<td>Report</td>
<td>Comorbidity</td>
<td>Age/SEX</td>
<td>APR dose</td>
<td>Bas PASI</td>
<td>Tx outcome</td>
<td>AEs</td>
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</tr>
<tr>
<td>Carpentieri 2020 [43]</td>
<td>Malignancy (excl. NMSC): 10</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>Most patients showed improvement</td>
<td>no clinical or radiographic recurrence or progression of their cancer</td>
</tr>
<tr>
<td>Peitsch 2019 [44]</td>
<td>Mantel cell lymphoma under rituximab, hepatic and pulmonary aspergillosis</td>
<td>60, M</td>
<td>30 mg bid</td>
<td>17.2</td>
<td>PASI90 M5</td>
<td>None, lymphoma in remission</td>
</tr>
<tr>
<td>Takama 2020 [45]</td>
<td>Urinary bladder cancer under pembrolizumab</td>
<td>74, M</td>
<td>30 mg bid</td>
<td>2.9</td>
<td>PASI50 W2, PASI90 M2</td>
<td>Nausea</td>
</tr>
<tr>
<td>Foti 2021 [46]</td>
<td>Melanoma with lymph node metastasis under nivolumab</td>
<td>62, M</td>
<td>30 mg bid</td>
<td>44</td>
<td>PASI50 M6, PASI90 M12</td>
<td>No, no worsening of melanoma</td>
</tr>
<tr>
<td>Di Lernia 2021 [47]</td>
<td>Malignancy: 3 colorectal, 2 GI stromal, 1 leukemia, 1 lymphoma, 1 kidney, 1</td>
<td>5 F, 9 M</td>
<td>30 mg bid</td>
<td>N/R</td>
<td>N/R</td>
<td>Diarrhea, headache (3 patients, disc. APR), urinary bladder cancer and metastatic SCC recurrence after APR disc.</td>
</tr>
<tr>
<td>Aragon-Miguel 2019 [48]</td>
<td>Malignancy hx: 6, latent tuberculosis: 16, hepatitis C or B (chronic or past): 7</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R, No infection reactivations</td>
</tr>
<tr>
<td>Tampouratzi 2019 [49]</td>
<td>Chronic hepatitis B, under entecavir</td>
<td>64, M</td>
<td>N/R</td>
<td>N/R</td>
<td>Excellent response</td>
<td>None</td>
</tr>
<tr>
<td>Papadavid 2018 [50]</td>
<td>Malignancy hx: 1, latent tuberculosis: 1, chronic latent hepatitis B: 1</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Sahuquillo-Torralba 2020 [51]</td>
<td>Latent tuberculosis: 1, active hepatitis B: 1, spontaneous bacterial peritonitis: 1, immune hepatitis: 1</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Siciliano 2020 [52]</td>
<td>Metastatic melanoma (2018)</td>
<td>75, M</td>
<td>30 mg bid</td>
<td>N/R</td>
<td>Improvement</td>
<td>None, melanoma remission</td>
</tr>
<tr>
<td>Lanna 2020 [53]</td>
<td>Tumors: 5</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>None</td>
</tr>
<tr>
<td>Lanna 2019 [54]</td>
<td>Hepatitis E</td>
<td>55, M</td>
<td>30 mg bid</td>
<td>18</td>
<td>PASI90 M6</td>
<td>None</td>
</tr>
<tr>
<td>Balato 2020 [55]</td>
<td>Malignancy: 40</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>Lower PASI50 and PASI75 response rates</td>
</tr>
<tr>
<td>Ighani 2018 (1) [56]</td>
<td>Malignancy hx: 15, liver disease: 8, psychiatric disorder: 9</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Ighani 2018 (2) [57]</td>
<td>Malignancy hx: 31, liver disease: 27, psychiatric disorder: 29</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Report</td>
<td>Comorbidity</td>
<td>Age/Sex</td>
<td>APR dose</td>
<td>Bas PASI</td>
<td>Tx outcome</td>
<td>AEs</td>
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<tr>
<td>Ighani 2018 (3) [58]</td>
<td>Malignancy hx: 5, liver disease: 4, psychiatric disorder: 4</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Phan 2020 [59]</td>
<td>Malignancy: 40</td>
<td>&gt;65 y</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Ighani 2018 (4) [60]</td>
<td>hepatitis C: 2, breast cancer: 2, renal disease (unspecified): 2</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Megna 2020 [61]</td>
<td>Malignancy: 9, hepatitis C: 4, latent tuberculosis: 3</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Del Alcázar 2020 [62]</td>
<td>Lung cancer: 20, latent tuberculosis: 20, hepatitis C: 17, hepatitis B: 13, hepatitis B and C: 2, malignancy hx: 92, liver disease: 33</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>No cases of infection reactivation or cancer recurrence</td>
</tr>
<tr>
<td>Fremlin 2017 [63]</td>
<td>Cases of alcohol excess, alcoholic liver disease, previous malignancy (unspecified number)</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Foulkes 2017 [64]</td>
<td>Cases of malignant melanoma and HIV (unspecified number)</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Malara 2018 [65]</td>
<td>Latent tubercular skin infection: 2, previous hepatitis: 1, endocarditis-related cardiac valve failure: 1, malignancy: 4</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>None</td>
</tr>
<tr>
<td>Daudén 2020 [14]</td>
<td>Malignancy hx: 14 (6 in last 5 years), hepatitis B:12, hepatitis C: 5, chronic liver disease: 20, renal insufficiency: 3</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Kungurov 2019 [66]</td>
<td>Hepatitis B: 1, chronic pancreatitis, cholecystitis and colitis: 1, hepatitis C: 1</td>
<td>47, F; 38, F; 31, M</td>
<td>N/R</td>
<td>27.3; 29.9; 33</td>
<td>PASI75 W24; PASI75 W6; PASI75 W28</td>
<td>None</td>
</tr>
<tr>
<td>Aragon-Miguel 2019 [67]</td>
<td>breast cancer: 1, gallbladder cancer: 1, treated latent tuberculosis: 3</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Bulic 2019 [68]</td>
<td>1. laryngeal SCC (2013) 2. papillary thyroid cancer (2014) 3. liver cirrhosis (Child-Pugh B)/portal hypertension/hepatocellular cancer (pT2pNxpMx)/liver transplant (2017) 4. melanoma (pT1a, Breslow 0.81mm) (2013)</td>
<td>51, M; 50, M; 51, M; 58, F</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>No recurrency of malignancy over a two-year follow-up</td>
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<tr>
<td>Fattore 2019 [69]</td>
<td>Non-metastatic non-small-cell lung cancer under nivolumab</td>
<td>74, F</td>
<td>30 mg bid</td>
<td>N/R</td>
<td>PASI100 W6</td>
<td>Transient nausea</td>
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<tr>
<td>Magdaleno 2019 [70]</td>
<td>Chronic liver disease: 13, severe infection: 11, previous malignancy: 8</td>
<td>N/R</td>
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<tr>
<td>Report</td>
<td>Comorbidity</td>
<td>Age/Sex</td>
<td>APR dose</td>
<td>Bas PASI</td>
<td>Tx outcome</td>
<td>AEs</td>
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<tr>
<td>Magdaleno-Tapial 2019 [71]</td>
<td>Chronic active alcoholism and hyper-transaminasemia</td>
<td>61, M</td>
<td>N/R</td>
<td>N/R</td>
<td>PASI&lt;5 M6</td>
<td>No serious AEs</td>
</tr>
<tr>
<td>Gioe 2021 [72]</td>
<td>Chronic hepatitis B, bipolar disorder, acute MRSA bacteremia, pulmonary embolus</td>
<td>34, F</td>
<td>N/R</td>
<td>N/R (&gt;95% BSA)</td>
<td>BSA&lt; 15% M1</td>
<td>N/R</td>
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</table>
| Ibarguren 2021 [73]           | 1. Stage IV uveal melanoma  
2. Stage IV laryngeal carcinoma  
3. Stage IV squamous cell lung carcinoma  
all 3 under nivolumab        | 50, M   | 30 mg bid | 12       | PASI50 M12 | 1. diarrhea  
2. headache, cancer progression after 10 months  
3. cancer progression after 10 months |
|                               |                                                                           | 70, M   | 13.8     |          | PASI75 (time N/R) |                                              |
|                               |                                                                           | 60, M   | 6.4      |          | PASI50 not achieved |                                              |
| Kurata 2021 [74]              | Colorectal cancer within past year                                       | 82, F   | N/R      | 5.5      | PASI90 and NAPSI50 W8 | γ-GT increase after 8 weeks & drug disc.        |

AEs = adverse events; APR = apremilast; Bas = baseline; bid = twice daily; BSA = body surface area; F = female; CLL = chronic lymphocytic leukemia; disc. = discontinuation; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hx = history; LFTs = liver function tests; M = male; M = month; MRSA = methicillin resistant staphylococcus aureus; NAPSI = nail psoriasis severity index; NMSC = non-melanoma skin cancer; N/R = not reported; od = once daily; PASI = Psoriasis Area and Severity Index; PASI50 = 50% reduction of baseline PASI; PASI75 = 75% reduction of baseline PASI; PASI90 = 90% reduction of baseline PASI; PASI100 = 100% reduction of baseline PASI; PSSI = psoriasis scalp severity index; SCC = squamous cell carcinoma; Tx = treatment; y = years old; URTIs = upper respiratory tract infections; W = week.
Table 3. Methodological quality assessment of included reports.

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Case reports have been assessed through the JBI critical appraisal checklist for case reports. Cross-sectional studies have been assessed through the NIH quality assessment tool for observational cohort and cross-sectional studies. Each report has been assigned an overall quality marking of poor, good or fair.
small molecules like apremilast are thought to be immuno-suppressed [6]. There have been reports of asymptomatic, as well as of fast and uneventful resolution of COVID-19 infections in psoriasis patients under apremilast, even in the case of serious comorbidities [21-23]. What is more, it seems that apremilast use does not hinder the formation of antibodies against SARS-CoV-2 [6]. It is important to remember that common apremilast AEs like taste alteration and gastrointestinal symptoms can mimic COVID-19 manifestations [6].

A relatively new, special population of psoriatic patients are those receiving therapy with immune checkpoint inhibitors (ICPIs) for various types of cancer. ICPIs have revolutionized cancer treatment and their use expands constantly. They include monoclonal antibodies that target cytotoxic T lymphocyte–associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed death ligand 1 (PD-L1) [24]. Due to the unique nature of ICPIs, a new category of AEs emerged concurrently with their clinical use [24]. They are known as “immune-related adverse events” (irAEs) and although they can affect any organ, skin is the one most frequently involved [24]. Morbilliform eruptions, pruritus, vitiligo and lichenoid eruptions are by far the most common cutaneous irAEs [25, 26]. Numerous others have been reported, among which newly occurring or exacerbating previous psoriasis.

In the majority of cases, cutaneous irAEs are mild-to-moderate (grade 1-2) and anti-cancer treatment is not interrupted, although severity may vary, up to life-threatening Stevens-Johnson syndrome/toxic epidermal necrolysis [27,28]. Similarly, psoriasis is usually managed with topical treatment [24,29]. In moderate/severe cases, treatment is more complicated since immunosuppression by anti-psoriatic drugs can theoretically lead to tumor escape. In those patients, apremilast seems to be a relatively safe and effective choice, however its use is supported only by case reports/small case series. Finally, an algorithm published recently by the ENCADO (European Network for Cutaneous Adverse Event to Oncologic Drugs) also suggests apremilast if the patient does not respond to phototherapy and/or acitretin [30].

Our study is not without its limitations. A few large studies like Armstrong and Levi were excluded from this review and potentially significant data was missed, because results were not reported separately for patients receiving apremilast monotherapy and those receiving combination treatment or other systemic agents [31]. On the other hand, it is fairly possible that some patients included in this review have been counted more than once, as they might have been sourced from the same databases or research centers (eg multiple publications by the same authors, Table 2). What is more, in studies reporting on multiple patients, efficacy and safety outcome measures were usually presented indistinguishably for all included patients and not individually, based on the comorbidity status, therefore the relevant fields of Table 2 could not be filled in. Last but not least, baseline comorbidity cases such as chronic infections were sometimes presented as a total number, without distinguishing among different types of eg infections.

All in all, according to this case series and systematic review, real-life use of apremilast so far suggests that the latter is indeed a safe and adequately efficacious option for moderate-to-severe psoriasis that cannot be treated/is challenging to treat with classic systemic agents and/or biologics. What is more, there seems to be no increased risk of COVID-19 infection in patients receiving apremilast, with evidence suggesting a smoother course of the disease.

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14


Five Synchronous Melanomas: Role of Dermoscopy as a Triage Tool to Manage Melanoma During the COVID-19 Pandemic

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Key words: COVID-19, dermoscopy, management, in situ melanoma, synchronous melanomas


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Authorship: All authors have contributed significantly to this publication.

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Introduction

Multiple meta-analyses have shown that dermoscopy is more accurate than the naked eye in melanoma diagnosis [1]. Since dermoscopy has direct histopathological correlates, it can be used to triage and manage pigmented lesions [2]. Certain colors under dermoscopy such as blue over raised areas are indicators of deep melanin, whereas on flat surfaces may indicate regression [2]. Furthermore, certain structures indicate melanoma invasion such as shiny white streaks or blue-whitish veil [2]. Hence, when large lesions are challenging to be excised completely, these areas suspicious for invasion under dermoscopy such as raised blue-gray areas could be sampled in order to maximize the histologic results. Moreover, dermoscopy also allows the identification of small invasive melanomas thus improving its management. During our daily practice, currently in the middle of the COVID-19 pandemic, we face challenging cases that need to be managed with fewer visits than usual.

Case Presentation

An 89-year-old man with multiple comorbidities, ECOG 3, was referred for evaluation of a nasal pigmented lesion. Previous biopsies did not reveal malignancy but he referred enlargement over time. A brown-black 2.5 cm-patch with ill-defined borders covered patient’s central nasal dorsum (Figure 1A). Dermoscopy showed asymmetric pigment around follicles, peppering, angulated lines, and areas of follicle invasion (Figures 1, B, C and D). A complete cutaneous examination was performed identifying four further suspicious lesions. One black 2.1 x 1 cm macule on the chest (Figure 2A) showing peripheral streaks asymmetrically distributed and a central blue-whitish veil on dermoscopy (Figure 2B). One elongated...
Figure 1. (A) Clinical image of the nasal dorsum pigmented lesion consisting of a brown-black 2.5 cm patch with ill-defined borders that covers the central nasal dorsum. (B-D) Dermoscopy images showing asymmetric pigmented follicular openings (arrows), angulated or polygonal lines (arrowheads), blue-gray dots or peppering (asterisk), and areas of follicle invasion (circles).

Figure 2. (A) Clinical image of the 2.2 x 2 cm macule on the chest. (B) Dermoscopic image showing peripheral streaks asymmetrically distributed and central blue-whitish veil. (C) Clinical image of the pigmented lesion on the neck, which presented as an elongated brown-black macule of 1.4 x 0.8 cm. (D) Dermoscopy of the neck lesion where atypical pigmented network and an irregular black blotch at the periphery can be observed. (E) Clinical image of the upper dorsum brown to black 0.5 x 0.3 cm macule. (F) Upper dorsum lesion dermoscopy showing an atypical brown network. (G) Clinical image of the pigmented lesion on the right shoulder presented as a brown-black 0.7 x 0.6 cm macule. (H) Atypical brown network and inferior-left homogeneous brown area on dermoscopy of the shoulder lesion.
brown to black 1.4 x 0.8 cm macule on the neck (Figure 2C), with an atypical pigmented network and an irregular black blotch on dermoscopy (Figure 2D). A brown to black 0.5 x 0.3 cm macule on the upper dorsum showing an atypical brown network on dermoscopy (Figures 2, E and F). Ultimately, a brown to black 0.7 x 0.6 cm macule on his right shoulder, with an atypical brown network and an inferior-left homogenous brown area on dermoscopy (Figures 2, G and H).

Given the number of lesions suggesting melanoma and considering the patient comorbidities, a shave-excision was performed during the same initial appointment of the smaller lesions suspected to be in situ by dermoscopy (atypical network with absence of blue-gray color, shiny white structures or vessels): the shoulder and upper dorsum lesions. The patient was scheduled for complete excision of the chest and neck lesions, due to suspicion of invasion (blue-whitish veil on dermoscopy) on the former, and due to a larger size and irregular shape on the latter. Regarding the nasal lesion, although no signs of invasion were suspected, due to its large size and the potentially complex reconstruction, a dermoscopy-targeted punch biopsy was performed on the brown area, and not on the blue-gray area which may have only revealed regression.

Results from histologic examination yielded four in situ melanomas, and an invasive melanoma with a 0.6 mm Breslow index (chest lesion). Wide local excision was later performed in all lesions according to the current guidelines. The patient is alive with no signs of active disease.

Conclusions
We present an unusual case of a man with five synchronous primary melanomas, whose management was streamlined thanks to dermoscopy. Hence, by using dermoscopy we could simplify the patient flow and minimize the number of appointments, especially useful in the current context of COVID-19 pandemic.

References
Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase

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Key words: Granuloma Annulare, Covid-19, SARS-Cov-2, Palisading granuloma, Subcutaneous GA


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Introduction

Granuloma Annulare (GA) is a benign, self-limiting, chronic granulomatous disorder. Viruses are one of the triggering factors. Only two case reports of SARS-Cov-2 triggered GA are reported till date; one - in an adult (localized GA) and another localized, generalized and subcutaneous GA (SCGA) in pediatric patients [1,2]. SCGA is rare in adults, especially geriatric population.

Case Presentation

A 63-year-old male presented with abrupt onset, multiple, asymptomatic, skin-colored to erythematous nodules involving abdomen, bilateral upper and lower limbs for 7 days. Lesions progressed rapidly without systemic complaints except for malaise. Patient denied insect bite/ trauma before the onset. There was no ulceration/ discharge from the nodules. Twenty days earlier, he had fever, sore-throat, malaise, body-aches and anosmia (Positive Rapid Antigen test for SARS-Cov-2). Patient received symptomatic treatment (Paracetamol and Etoricoxib) under home-isolation. SARS-Cov-2 infection was also present in wife and daughter.

Clinically, there were 23 discrete, subcutaneous nodules, firm to hard, non-tender, non-fluctuant, mobile, symmetrically distributed predominantly over extensors of bilateral thighs and few on legs, upper-arms and abdomen. Majority were appreciated on palpation only while few lesions had erythematous hue. The largest lesion measured 4 x 3 cm² over right upper thigh whereas others varied from 1 x 1 to 1.5 x 2 cm² (Figure 1). Routine biochemistry, hemogram, anti-streptolysin O titres, and Mantoux test were normal. C-reactive protein and ESR were high. SARS-Cov-2 IgG titre was 64 AU/mL(positive). Serology for HBV, HCV,
HIV, Parvovirus-B19, HSV-1 and 2, EBV, CMV, Adenovirus, Mycoplasma pneumoniae, rickettsiosis were negative. Considering the age, he was investigated for any associated malignancy. CECT-Chest revealed subtle ground glass opacities in bilateral upper lobes and fibro-atelectatic bands in apical zones suggesting post-covid sequelae. CECT-Abdomen and pelvis were normal. Deep incisional skin biopsy considering differential diagnosis of Erythema Nodosum (EN), Subcutaneous Sweet Syndrome and SCGA was performed. Histopathology was consistent with SCGA (Figure 2). Alcian Blue staining was also positive for mucin. Intralesional triamcinolone acetonide (10mg/ml) was injected in divided sittings after informed consent from the patient resulting in complete remission within fifteen days.

Conclusions
SCGA commonly affects trauma-prone sites like extensors of distal extremities. In our case it involved proximal upper and lower extremities, and abdomen. Possibility of drugs inciting SCGA is unlikely as patient had taken Paracetamol and Etoricoxib in past without any dermatological complaints. The conspicuous absence of lesional pain, tenderness, erythema and concomitant systemic features ruled out EN and Sweet syndrome. Absence of vasculitis on histopathology eliminates causes of ‘septal panniculitis with vasculitis’. Histopathologically, positive Alcian blue stain for mucin excludes differential of Miescher Radial Granuloma of EN. Although, rheumatoid nodules are also asymptomatic and
simulates SCGA on histopathology, the former has more fibrin deposition than mucin causing ‘red’ granulomas unlike ‘blue’ granulomas in SCGA.

SARS-Cov-2 induces cytokine storm, producing IL-1β, IL-6, TNF-α, IL-12/23 which may precipitate SCGA as a reactive phenomenon. Vascular damage associated with viruses causing immune-complex deposition may also explain chronic granulomatous changes seen in GA. To conclude, geriatric SCGA may be another dermatological manifestation triggered by SARS-Cov-2. It may enforce a huge diagnostic dilemma in the elderly confusing it with cutaneous metastasis necessitating meticulous diagnostic workup.

References


Sexually Transmitted Infections During the COVID-19 Pandemic in a Swedish Healthcare Region Without Lockdown: A Focus On Gonorrhea and Syphilis

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Key words: syphilis, Covid-19, SARS-Cov-2, gonorrhea

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Introduction

In late December 2019, the first case of infection with SARS-CoV-2 was reported [1]. In March 2020, the pandemic was declared and led to the collapse of the health care functioning [2]. The normal access to specialist care was not always guaranteed in many countries around the world. In March 2020 the pandemic reached Sweden and the Public Health Agency of Sweden issued recommendations to people aged from 70 years or older and risk groups including physical distancing. The incidence of syphilis and gonorrhea in the COVID-19 pandemic in Sweden has not been studied yet in contrast to several other countries. Several studies reported a decrease in early syphilis and gonorrhea cases and one from the Czech Republic showed an initial decrease of early syphilis followed by a significant increase during the pandemic (March 2020 – February 2021)[3-6].

Case presentation

We aimed to compare the incidence of gonorrhea and syphilis in Region Jonkoping County healthcare region in Sweden during the 18-month COVID-19 period with the non-pandemic period. This was a retrospective, observational cohort study done in the three hospitals (Ryhov County Hospital, Highland Hospital of Nassjo, and Varnamo Hospital) in Region Jonkoping County (RJC), which is part of the southeast healthcare region in Sweden providing a healthcare for approximately 360,000 inhabitants. The study was a quality review study approved by the operations manager and Head of Department of Dermatology at Ryhov County Hospital in Jonkoping County Region according to Section 31 of the Health and Medical Services Act, which was published in Lakartidningen (2013; 112: C9CL).
We analyzed monthly cases of gonorrhea and syphilis at our three hospitals. We have observed a significant increase in syphilis cases during the pandemic (April 1, 2020 – September 31, 2021) compared to non-pandemic period (October 1, 2018 – March 31, 2020). The difference in the number of gonorrhea cases during pandemic versus non-pandemic was not significant. Twenty-five cases of syphilis were reported during the pandemic and only 10 syphilis cases during the non-pandemic period ($P = 0.0143$, 95% CI 1.20-5.20, RR 2.49). Forty-four gonorrhea cases were reported under the pandemic period and 52 gonorrhea cases under the non-pandemic period (Figure 1).

**Conclusions**

The effect of the pandemic on sexually transmitted diseases (STDs) frequency is difficult to explain due to differences in pandemic social restriction measures worldwide. The implementation of the measures was expected to reduce not only the spread of COVID-19 but also STDs. The incidence of syphilis and gonorrhea decreased during the pandemic according to reports from several countries with lockdown [3–5]. One study reported an increase in the incidence of syphilis when social measures were subsequently relaxed [6]. On contrary, the access to healthcare was not affected with the pandemic in Sweden, and the tracking of cases and partner notification was functioning as during the time before the pandemic. The increase in newly diagnosed syphilis cases during pandemic might be explained not only by light COVID-19 restrictions and poor compliance with recommendations for social distancing but also rising STDs trend.

**References**

Benefits and Pitfalls of Using in Vivo Reflectance Confocal Microscopy in Lentigo Maligna Diagnostics: Case Reports

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Key words: lentigo maligna, in vivo reflectance confocal microscopy, pigmented facial lesion, diagnostic accuracy


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Authorship: All authors have contributed significantly to this publication.
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Introduction

The differential diagnosis between lentigo maligna (LM) and pigmented facial lesions (PFL) might be challenging clinically and dermoscopically, especially in its early phases, because early melanoma may exhibit only subtle malignancy clues and may have overlapping features with PFL [1,2]. Therefore, new diagnostic tools such as Reflectance confocal microscopy (RCM) to improve early detection of LM in its initial growth phases are crucial. Herein reported two cases of LM and two different approaches of using RCM.

Case Presentation

A 47-year-old man presented at our department for laser treatment of some facial brownish macules. During routine examination using a dermatoscope a macule on the tip of the nose was noted (Figure 1A). Dermoscopically a structureless brownish color pigmentation and irregular grayish pigmentation around some follicles were present (Figure 1B). Due to the doubtful appearance in dermoscopy RCM examination was performed revealing the presence of several atypical melanocytes located mainly around hair follicles (Figure 1C). Based on confocal features, a total surgical excision was performed and a final diagnosis of LM was confirmed (Figure 1D). The patient refused the re-excision, and adjuvant therapy with Imiquimod 5% cream once daily for 6 weeks was started. After 2 years of follow up, no melanoma recurrence signs were noted.

A 61-year-old woman presented at our clinic for evaluation of a pigmented macule on the left cheek (Figure 2A). The patient had no previous history of melanoma. Both
clinically and dermoscopically (Figure 2B) the lesion looked suspicious. Under RCM examination atypical dendritic cells were visible at the level of the epidermis, they were not located around follicles nor infiltrating them. Melanocytic nests forming cords were visible at the level of the dermal-epidermal junction, with no obvious melanoma features (Figure 2C). However, due to the suspicious dermoscopic aspect, the lesion was excised and a final diagnosis of LM was confirmed by histology (Figure 2D). The patient is recurrence free after 2 years follow up.

Conclusions

In the first case presented, the lesion did not show any specific features for melanoma. On dermoscopy the only subtle suspicious clue was the presence of greyish color around some follicles. This clue shows high sensitivity (85, 1%) but quite low specificity (39, 7%) [1]. RCM helped us reveal characteristics suggestive of the melanocytic nature of the lesion.

In the second case the lesion both clinically and dermoscopically looked suspicious, however RCM findings were subtle. Indeed, on RCM, the lesion had regular epidermal architecture, which is noteworthy and in the early radial growth phase of melanoma, follicles were well defined without folliculotropism and widespread dendrites. In this case the confidence level of the dermatologist in making diagnosis of LM was higher with the dermatoscope. Therefore, this second case supported that clinical and dermoscopic criteria are extremely important for LM diagnosis.

In conclusion, LM diagnosis still remains challenging. A combined clinical/dermoscopic/confocal approach should be used for the management of PFL in order to provide a more conclusive pre-histological diagnosis leading clinicians to a correct management.
Figure 2. (A) Pigmented macule located on the left cheek (5 × 7 mm) with irregular borders and variegated color (red arrow). (B) Dermoscopy showing an asymmetric pigmented macule with atypical infiltration of interspaces and adnexal structures (red stars). (C) RCM mosaic (1.5 × 2.5 mm) at the level of the DEJ showing junctional nesting (red arrows) without colonization of atypical cells around hair follicles. (D) Histopathology: the sublesional dermis shows marked solar elastosis and increased melanophages (black arrow: melanocytic nest; red arrows: melanophages; black stars: solar elastosis) (H&E, ×200).
Dermatoscopic Features of Angiomatoid Spitz Nevus: a Case Report

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Key words: angiomatoid Spitz nevus, coiled vessels, dermoscopy, immunohistochemistry


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Introduction

Angiomatoid Spitz nevus (SN) is an uncommon histopathological variant of SN that is most frequently seen on the extremities of children and young adults. Dermatoscopic features of this unusual variant have rarely been reported [1,2]. We presented a 19-year-old female diagnosed with angiomatoid SN based on the clinical, dermatoscopic, and histopathological findings.

Case Presentation

An otherwise healthy 19-year-old female presented with an asymptomatic, slowly growing, nodule for 4 months. Physical examination demonstrated an exophytic, non-tender, erythematous nodule 0.8 x 0.6 cm in diameter on the right pretibial region (Figure 1A). Medical history and systematic review were unremarkable. Polarized-light dermatoscopic examination showed a red structureless background, white lines reticular, numerous coiled vessels without specific arrangement, and surface scale (Figure 1B). The lesion was totally excised with the preliminary diagnoses of hemangioma, SN, dermatofibroma, amelanotic melanoma, and eccrine poroma. Histopathological examination showed a symmetrical lesion composed of predominantly spindle and less often epithelioid cells containing eosinophilic cytoplasm. The cells were distributed mostly in vertically oriented nests along the dermo-epidermal junction. Maturation to the depth was evident. There were numerous superficial small and thin-walled blood vessels within the fibrotic collagen bundles. A dense, diffuse lymphocyte-predominant inflammatory infiltrate was also observed (Figure 1, C and D; Figure 2A). No significant atypia and mitotic activity were detected. Immunohistochemical staining HMB-45 (Figure 2B) and Melan-A were focally positive within the superficial dermal nests, while p16 (Figure 2C) and S100 showed diffuse positivity. A diagnosis of angiomatoid SN was made based on the clinical, dermatoscopic, histopathological and immunohistochemical features.
Figure 1. (A) A hemangioma-like dome-shaped nodular lesion on the right pretibial region. (B) Dermatoscopy revealed red structureless background, white lines reticular, coiled vessels without specific arrangement and surface scale. (C;D) Histopathological sections showed hyperkeratosis, hypergranulosis, vertically-oriented nests mainly composed of spindle cells and numerous small and thin walled blood vessels within the superficial dermis (H&E, x50).

Figure 2. (A) The tumor cells show maturation with depth and break up into single melanocytes at the base of the lesion (H&E, x50). (B) HMB45 antibody showed staining confined to junctional and superficial dermal component (x50). (C) The lesion showed diffuse and strongly positive staining for p16 (x50).
The consent form was taken from the patient.

Conclusions

SN may present with a wide spectrum of clinical and histopathological appearance. Desmoplastic, angiomatoid, verrucous/polypoid, plexiform, pagetoid, halo, myxoid, granulomatous, and tubular variants have been described in the relevant literature [1]. Angiomatoid SN is characterized by marked proliferation of blood vessels around the intradermal melanocytes of SN and clinically manifests as a hemangioma-like nodular lesion.

Moscarella et al. reported a total of 307 cutaneous lesions with a histopathological diagnosis of Spitz/Reed nevus. Five out of them were angiomatoid Spitz nevus which are dermatoscopically showed different combinations of central pink to white areas, milky red color, peripheral network, brown to grey streaks, dotted vessels, and linear vessels [1]. Anju et al also reported a case of angiomatoid SN dermatoscopically characterized by reddish homogeneous area with scales and dotted linear pigmentation [2]. Our case exhibited white lines reticular and coiled vessels that were not observed in the aforementioned studies [1]. Red structureless areas and coiled vessels observed in the present case reflect the proliferation of superficial dermal vessels and inflammation while white lines reticular correspond with fibrotic collagen bundles.

Although the dermatoscopic findings we described in this case can be observed in SN in general, we believe that the predominancy of coiled vessels may be an important clue to the angiomatoid variant of SN.

References

Dupilumab-associated Facial Erythema Successfully Treated With Oral Ivermectin

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Key words: dupilumab, facial dermatitis, atopic dermatitis, ivermectin

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Introduction

Dupilumab, a monoclonal antibody which inhibits IL-4 and IL-13 signaling, has revolutionized atopic dermatitis (AD) treatment. Dupilumab-associated facial erythema (DFE) has been described in 10% of patients and can lead to dupilumab discontinuation [1]. Etiology remains unclear and treatment is challenging [1-3]. Here we present a patient with DFE successfully treated with oral ivermectin.

Case Presentation

A 20-year-old woman with severe AD, refractory to cyclosporine, started dupilumab. After 6 weeks, although AD lesions had resolved, she manifested itching and facial erythema which were not previously present. On physical examination, scaly ill-defined erythematous plaques were observed on the forehead and cheeks. Dermoscopy showed small pustules (Figure 1 A and B). DFE was diagnosed. No patch tests were performed. There was no response to topical corticosteroids or tacrolimus with local adverse effects (AE), nor to oral itraconazole and topical ketoconazole. Since small pustules were present on dermoscopy, dupilumab-associated rosacea was suspected. To avoid local AE, a single dose of oral ivermectin 200 mcg/kg (12 mg) was prescribed. The patient presented a complete resolution of facial erythema in 3 weeks, which has been maintained after 14 months of follow-up (Figure 2).

Conclusions

Face and neck dermatitis (FND) in atopic dermatitis is a diagnostic challenge in which dupilumab adds a new grade of complexity [2]. In a recent systematic review of 101 patients with DFE, 45% of patients reported different cutaneous symptoms from preexisting atopic dermatitis [3]. Diverse etiologies for DFE have been proposed, including worsening of AD, allergic contact dermatitis (ACD), rosacea, topical corticoids withdrawal (TCW), Malassezia furfur (MF) hypersensitivity and alcohol-induced facial flushing [2-4].
In a retrospective study of 94 patients with dupilumab [4], 6% presented rosacea-like folliculitis and increased demodex count in reflectance confocal microscopy [1,4]. Although DFE pathogenesis remains unclear, recent studies have hypothesized that IL-4 blockage shifts Th1/Th2 balance towards Th1/Th17-mediated dermatoses [2]. In rosacea, especially if papulopustular, the main factors are induction of Demodex proliferation by Th2 blockade and Th17-inflammatory response [1].

Regarding DFE treatment, topical corticosteroids and calcineurin inhibitors are the most used, although with low response rates. However, management of DFE should start with a precise differential diagnosis, since ACD, rosacea, TCW and MF-dermatitis respond to different approaches [2, 5]. Thus, most treatment failures could be explained by DFE being erroneously thought of as a unique entity. Evidence on rosacea-like dermatitis treatment remains sparse [2]. Partial or complete response to acaricidal agents such as topical and oral metronidazole, topical ivermectin or doxycycline have been reported [2]. Topical ivermectin is a first-line therapy for papulopustular rosacea, although it requires prolonged treatment (up to 12 weeks). Oral ivermectin treatment for rosacea has been reported in isolated cases with satisfactory results. It has very low systemic AE (<1%) and two main advantages: single administration schedule and avoidance of local AE.

In patients under treatment with dupilumab presenting with facial erythema, DFE should be considered. Rather than a unique entity, DFE should be considered as a compendium of differential diagnoses. If rosacea-like dermatitis is suspected, oral ivermectin could represent a good and well-tolerated alternative.

References


Introduction

Alopecia areata (AA) is a non-scarring disorder of the hair follicle and currently pathogenesis research is focused on determining the role, contribution, and interactions between each of the immune components involved. It has been previously reported that fungal infection, seasonal airborne allergens, and other allergens may contribute to the complex autoimmune pathways of AA [1,2]. Recently, allergy to dust mite was associated with time of onset and severity of AA [3]. Thus, and in order to examine a possible contributing role of allergic contact dermatitis (ACD) in patients with AA, we performed patch testing in patients diagnosed with AA in our clinic.

Case presentation

Thirty-one patients, 12 males and 19 females, aged 18 to 83 years, firstly diagnosed with active AA lesions (positive hair pull test) were eligible for inclusion. Patients with personal history of atopic dermatitis (AD) and/or ACD were excluded from the study, to diminish possible bias effect. According to the International Contact Dermatitis Research Group guidelines, the European Baseline Series S-100 patch tests consisting of 32 allergens were performed as per protocol, after receiving informed consent from the participants. The interpretation of results was conducted in two consecutive visits, after 48 and 96 hours, to determine late allergic reactions.

Two patients (6.4%, 2/31) were found positive towards nickel, 1 patient (3.2%, 1/31) had a positive reaction against methylisothiazolinone and 1 patient (3.2%, 1/31) was positive against the fragrance mix. Since there was no control group, we can only report frequency of ACD in patients with AA.

Conclusions

The hair follicle is characterized by immune privilege, which protects it from being exposed to immune recognition, especially...
during anagen phase of hair growth. Immune privilege collapse is considered as the starting point of an immunologic cascade resulting in AA. However, it remains unclear which is the triggering event leading to excessive release of INF-γ in the microenvironment around the hair follicle in patients with AA.

ACD is a disease with genetic predisposition that is phenotypically expressed after the patient’s exposure to certain environmental factors. INF-γ, among other cytokines, is secreted not only during the sensitization but also during the elicitation phase of ACD [4]. Furthermore, Attia et al. reported that in patients with alopecia universalis IgE serum levels were higher than in patients with other types of AA [5].

The rate of ACD among AA patients in our series roughly conforms with the rate reported in the general population [4]. Patients with a history of AD were excluded, since those patients have shown to have higher rates of positive patch tests compared to the general population [6].

In conclusion, we could not detect a difference in the incidence of ACD in our group of patients. We acknowledge the fact that the sample size is limited, and clearly state that larger studies are needed to clarify the precise ratio and investigate a potential role of ACD in the susceptibility and/or onset of the immunologic phenomena involved in AA.

References

Dermatologic Manifestations of Thymoma-associated Multiorgan Autoimmunity (TAMA) Syndrome: Cutaneous Signs of an Immune Dysregulation

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Key words: TAMA syndrome, myastenia gravis, GVHD, thymoma


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Introduction

Thymoma-associated multiorgan autoimmunity (TAMA) syndrome is the consequence of auto-reactive T-cells activation developing in the setting of a thymoma, which mediates graft-versus-host-disease (GHVD)-like reactions in several tissues, including skin [1].

Case Presentation

A 61-year-old man was admitted in our Dermatology Department for a skin rash appearing concomitantly to a nodal relapse of a malignant thymoma. Cutaneous examination revealed a confluent erythematous and papulo-squamous eruption involving most of his face, trunk, bilateral upper and lower extremities. His palms and soles presented confluent pink tender papules. Moreover, multiple chronic painful erosions affected the oral mucosa (Figure 1). The patient reported general malaise with deep asthenia and an abundant chronic diarrhea.

A skin biopsy was performed and histologic examination revealed an interface and perivascular dermatitis in the dermis. Epidermis showed psoriasiform hyperplasia, diffuse parakeratosis and spongiosis, hypogranulosis, necrotic keratinocytes with intense eosinophilic cytoplasm (Figure 2). Although several differential diagnoses (including drug reaction, viral exanthema, pityriasis lichenoid, and sub-erytrodermic psoriasis) were considered, relying on
In addition, our patient developed a progressive muscle weakness. A thymoma-related myasthenia gravis was diagnosed after the detection of autoantibodies directed against
acetylcholine receptor and electrophysiological evaluation of neuromuscular junctions.

After three months our patient died as a result of the rapidly progressive clinical deterioration and the hypoxemic respiratory failure consequent to a lung infection and myasthenia gravis.

Myasthenia gravis is the most typical paraneoplastic syndrome associated with thymoma; it does not always develop at diagnosis, but it has a high impact of morbidity and mortality [2].

GVHD-like reactions are rare immune response that occur particularly at level of skin, intestine, or liver, which resemble GVHD on histopathology, except for graft lymphocytes [3]. The diagnosis requires the exclusion of the main causes of a real GHVD, such as hematopoietic stem cell transplantation (HSCT) and transfusion of non-irradiated blood. Being not associated to HSCT, Waldhera et al decided to collect the GVHD-like reactions occurred in the setting of a thymoma under the umbrella name of TAMA syndrome [1]. First described cases were characterized by a constant colon involvement; subsequently, TAMA reactions were detected in multiple organs, including not only gastrointestinal tract, but also skin, thyroid and liver [4].

Conclusions

We remark the uniqueness and interest of this case, since TAMA syndrome is a very rare disorder and with few cases reported in literature to date. The dermatologic manifestations of TAMA syndrome consist of diffuse papulo-squamous rash, often involving palms and soles, with possible lesions of oral mucosa. TAMA syndrome should be always kept in mind on a thymoma background when these specific skin signs are associated with systemic manifestations, first of all diarrhea.

References

Primary Cutaneous Follicle Center B-cell Lymphoma at the Site of a Resolved Herpes Zoster Eruption

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Key words: herpes zoster, lymphoma, clobetasol, Wolf response


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Introduction

In this report we describe the occurrence of a primary cutaneous follicle center B lymphoma in a skin area which had been previously affected by a herpes zoster eruption. The rarity of this phenomenon and its complete remission with topical steroid monotherapy make this report quite remarkable.

Case Presentation

We present the case of a 73-year-old man who came for the first time to our Dermatology Unit in 2019 for a burning and stinging blistering eruption on the left scapular area with a metameric distribution, highly indicative for a herpes zoster outbreak. We treated him with acyclovir 800 mg five times daily for seven days with a complete resolution of lesions.

After seven months the patient returned complaining about the development of six infiltrated plaques on the left scapular region, whose distribution was perfectly overlapping with the resolved shingles eruption (Figure 1A).

A biopsy was performed, and the histologic specimen showed a proliferation of neoplastic follicle center cells invading the entire dermis (Figure 2). Epidermis was spared and separated from the proliferating lymphocytes by a grenz zone in the upper dermis. B-cell immunohistochemistry was positive for CD20 and Bcl6 and only weakly positive for Bcl2. Furthermore, PCR demonstrated monoclonal immunoglobulin heavy chain gene rearrangement. Thus, a diagnosis of cutaneous follicle center lymphoma was made.

The patient had no medical history of malignancy, and his only comorbidity was hypertension. A PET-TC was performed to complete the staging and it resulted negative. This outcome justified a conservative approach, therefore we prescribed clobetasol propionate topical ointment 0.05% one application per day to treat the skin lesions. After 6 weeks, all lesions were already in complete remission (Figure 1B).
Conclusions

The occurrence of a skin disease in an area which had previously been affected by another unrelated dermatosis is known as Wolf isotopic response. This phenomenon often occurs with VZV infection representing the “first hit” [1].

The second dermatosis is usually a granulomatous or lichenoid manifestation, however infiltrations by hematologic malignancies, skin tumors, and infections have been described as well [1]. Although unfrequently, also pseudo-lymphomatous infiltrates have been observed in the area of a former herpes zoster [1], while the onset of primary cutaneous lymphomas in this setting is only anecdotal [2].

In order to explain this phenomenon, it has been suggested that varicella-zoster virus (VZV) infection might cause an abnormal lymphocytic activation; however, only in isolated cases VZV DNA was found in the histologic specimen [1,2]. An additional explanation might be that VZV infection locally reduces the immune surveillance, thereby facilitating the onset of neoplasms in the affected area [1].

In this report we have described the appearance of a primary cutaneous follicular B-cell lymphoma in the same area where a shingles outbreak had occurred 7 months before. One similar case already described in literature regarded a centrocytic/centroblastic lymphoma which was treated with systemic interferon alpha obtaining only partial remission [2]. In contrast, our case went into stable remission after application of topical steroids alone and to date no recurrence was observed after 14 months of follow-up, suggesting that clobetasol monotherapy might represent a valid treatment option for this kind of cutaneous neoplasm.

References

Mycoplasma Pneumoniae-associated Subcorneal Pustular Dermatosis: Not as Rare as We Think?

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Key words: Mycoplasma pneumoniae, subcorneal pustular dermatosis, Sneddon-Wilkinson disease, pustular eruption


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Introduction

Subcorneal pustular dermatosis (SPD) or Sneddon-Wilkinson disease is a rare condition included in the spectrum of neutrophilic dermatoses. Seldom it can be triggered by infections caused by Mycoplasma pneumoniae (MP) [1]. Herein we present the case of a young woman with SPD associated with an otherwise asymptomatic MP infection. Topical corticosteroids resolved lesions with no relapses after one-year follow-up.

Case Presentation

A 40-year-old woman presented with a two-week history of asymptomatic skin lesions located on the cervical, axillary, inframammary and inguinal folds, with no improvement despite treatment with topical clotrimazole and oral fluconazole. She felt otherwise well and reported no other symptoms. She was diagnosed with irritative eczema and treated with 0.5 mg/kg daily oral prednisone with clinical worsening a few days later. Clinical examination revealed well-demarcated non-infiltrated erythematous plaques with multiple fragile pustules measuring less than 1 mm over them, located on the aforementioned folds (Figure 1), some of them with annular and polycyclic borders. Physical examination was otherwise unremarkable. Oral prednisone was immediately switched to mometasone furoate 0.1% cream twice a day. Skin samples were culture-negative for bacterial and fungal pathogens and blood tests showed positive MP IgM and negative IgG. Skin biopsy (Figure 2) showed a subcorneal pustule filled with neutrophils, neutrophilic exocytosis below the pustule without other prominent epidermal changes, and dermal perivascular and interstitial infiltrate composed by neutrophils and lymphocytes. Direct immunofluorescence was negative, and no fungal structures were observed with PAS stain. These histological features were consistent with that of subcorneal pustular dermatosis. A few weeks later, blood tests demonstrated MP IgG seroconversion. After 15 days with topical mometasone the skin lesions had completely healed. With a diagnosis of MP-associated SPD, the patient was followed up for 1 year, with no recurrence.
Conclusions

MP-associated SPD has been previously reported by Winnock et al in a 43-year-old male, Papini et al in an 8-year-old male, Bohelay et al in a 19-year-old male and Lombart et al in a 36-year-old woman [2-5]. All the patients were young like our case, and MP infection clinical manifestations varied: some patients had a mild cough while others suffered pneumonia that required inpatient treatment. A few days later, the patients developed the skin manifestations

Figure 1. Clinical examination: large well-demarcated erythematous plaques with annular and polycyclic borders involving axillary and inframammary folds, with pustules measuring less than 1 mm.

Figure 2. H&E x20. Skin biopsy suggestive of subcorneal pustular dermatosis. A subcorneal pustule with neutrophilic exocytosis in the epidermis below it is observed, with no other remarkable epidermal changes; neutrophilic and lymphocytic dermal perivascular and interstitial infiltrate.
compatible with SPD. Winnock and Papini patients’ were treated with oral dapsone with resolution of the skin lesions in 1-3 months, and Bohelay and Lombart patients’ were treated with topical corticosteroids with improvement in 5-15 days, similarly to our case [2-5]. None of the patients suffered a relapse during follow-up [2-5]. These findings suggest that MP-SPD may require a different approach than “classical” SPD, for these patients have self-limiting and non-relapsing disease. Thus, we propose topical corticosteroids as a first-line therapy; oral dapsone could be reserved for unresponsive or serious cases. A scheduled follow-up visit may be unnecessary. As stated by Bohelay and Lombart MP is probably an underestimated trigger for SPD, given the asymptomatic course of the infection in many cases like our patient [4,5].

Even without symptoms of infection, laboratory testing for MP should be performed in young patients with SPD, as it may change the clinical approach to the patient, thus avoiding unnecessary systemic treatment and follow-up.

References

Dermoscopy of Lymphoplasmacellular Erosive Dermatitis of the Scalp Reveals Striking Similarities to Lymphoplasmacellular Balanitis of Zoon

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Key words: scalp dermatitis, lymphoplasmacellular dermatitis, erosive dermatitis, dermoscopy

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Introduction

We describe an erosive dermatitis of the scalp characterized by a prominent inflammatory lymphoplasmacellular infiltrate and presenting orange structureless areas with linear vessels on dermoscopy.

Case Presentation

We herein report a case series of 4 male patients, aged 77-86 years, presenting non-tender eroded plaques and crusts on the scalp, persisting for several weeks. They all showed androgenic alopecia and actinic damage, reporting history of actinic keratoses and squamous or basal cell carcinomas. On dermoscopy, the eroded lesions showed red-orange structureless areas with tortuous and telangiectatic linear vessels, together with white-yellow scales and crusts (Figure 1). Biopsies were performed and histopathological examination showed a prominent lymphoplasmacellular infiltrate in both reticular and superficial dermis (Figure 2), together with admixed eosinophils, neutrophils and mast cells and intraepidermal spongiosis. The histopathological picture suggested therefore a subacute dermatitis that we called ‘lymphoplasmacellular erosive dermatitis of the scalp’ (LEDS). All patients were treated for 25-30 days with betamethasone 0.1% and fusidic acid 2% cream (twice daily), obtaining complete response.

Conclusions

Our case series underlines that differential diagnosis of eroded lesions and crusts on the scalp can be sometimes troublesome: neoplastic diseases should be primarily excluded, but LEDS should be considered among other entities (Table 1) [1,2].

LEDS seems to share many aspects with erosive pustular dermatosis of the scalp (EPDS), such as advanced age, actinic damage, history of previous trauma/surgery [3,4].
Histopathologically, classical EPDS shows a mixed inflammatory infiltrate, with lymphocytes, plasma cells, and neutrophils, often forming pustules [3]. Instead, a predominant lymphoplasmacellular infiltrate is not a classic histopathological feature of EPDS, but biopsy timing as well as local and systemic immunological factors could play a role in determining this appearance. On dermoscopy, EPDS shows serum-hematic crusts, loss of follicular ostia and hair tufting, enlargement of dermal vessels and visualization of hair bulbs through a thinned skin [3], milky-red and white areas, linear but also polymorphous vessels [1]. Instead, in our cases we observed a remarkable orange structureless background with focused linear vessels. Notably, this dermoscopic pattern has been linked to the so called idiopathic lymphoplasmacellular mucositis-dermatitis (ILPMD), a group of disorders presenting a dense non-neoplastic plasma-cell infiltrate of uncertain etiology, that usually affect mucosal areas such as genitalia (typified by Zoon balanitis/vulvitis) [5,6]. Orange areas can be observed in several conditions, including those characterized by a dense/compact cellular infiltrate, causing the so-called ‘mass effect’, such as granulomatous dermatoses. Notably, in these cases, vessels are usually well-focused as the dermal infiltrate/deposit pushes them toward the skin surface [7]. Interestingly, the orange hue in Zoon balanitis has been attributed to hemosiderin deposits [6], but could also be due to the aforementioned ‘mass effect’. In addition, another relevant similarity between LEDS and Zoon balanitis is the clinical course, with response to topical steroid administration and frequent recurrences [4].

In conclusion, while LEDS could be interpreted as a variant of EPDS, the peculiar dermoscopic findings (orange structureless areas and linear vessels) apparently related to distinctive histological features (dense lymphoplasmacellular infiltrate) suggest that LEDS may be also categorized within the spectrum of chronic idiopathic lymphoplasmacellular dermatitis. Further investigations on a larger number of cases are needed to better define this entity.
### Table 1. Differential diagnoses of entities presenting with eroded lesions and crusts on the scalp: description of dermoscopic features and useful clues.

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Dermoscopic appearance</th>
<th>Clues and other features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neoplastic diseases (if ulcerated)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>Presence of typical signs such as on-focus arborizing vessels, blue-grey ovoid nests and globules/dots, brown spoke wheel or leaf like areas, ulcerations or erosions, shine white streaks, structureless white to red areas [2]</td>
<td>Relatively frequent on scalp presenting actinic damage; diagnosis can be more easily assessed focusing on non-ulcerated areas [2]</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Red structureless areas with polymorphous vessels (linear, hairpin or glomerular vessels), ulcerations, white halos surrounding vascular structures, white-yellow to light brown structureless areas (keratin), targetoid-appearing hair follicles (white circles) [2]</td>
<td>Relatively frequent on scalp presenting actinic damage; differential diagnosis may be difficult, in particular with poorly differentiated squamous cell carcinoma [2]</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>Milky-red and shiny white areas, pink or purple hue, polymorphous vessels (often linear irregular, dotted, arborizing or glomerular vessels), ulcerations [1]</td>
<td>Very rapid growth [1]</td>
</tr>
<tr>
<td>Amelanotic melanoma</td>
<td>Pigment remnants, milky red areas, more than one shade of pink, white structures, polymorphous vessels (more often linear irregular and dotted, but also hairpin vessel), ulcerations [2]</td>
<td>Often shows pigment remnants that can be a very useful diagnostic clue [2]</td>
</tr>
<tr>
<td>Atypical fibroxanthoma</td>
<td>Pink-red and white structureless areas, linear irregular vessels, white lines, ulcerations [1]</td>
<td>Rapid growth [1]</td>
</tr>
<tr>
<td><strong>Inflammatory diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic erosive pustular dermatosis of the scalp</td>
<td>Crusts, erosions, milky red areas, on-focus polymorphous vessels, hair tufting, skin atrophy (visualization of dermal vessels and hair bulbs) [1,3]</td>
<td>Shares many clinical and dermoscopic features with lymphoplasmacellular erosive dermatitis of the scalp [1,3]</td>
</tr>
<tr>
<td>Bullous diseases such as localized cicatricial bullous pemphigoid (Brunsting Perry disease) and pemphigus vulgaris</td>
<td>Erosions and scarring alopecia; acantholytic hair casts in pemphigus vulgaris [1]</td>
<td>Subepidermal blisters (Bursting Perry disease) or intraepidermal blisters (pemphigus vulgaris). Direct immunofluorescence and circulating antibody tests are useful. Pemphigus vulgaris often involves other body areas [1]</td>
</tr>
<tr>
<td>Severe bacterial or fungal infection</td>
<td>Perifollicular pustules, purulent discharge; hair change in fungal infection (black dots, broken hairs, comma hairs, corkscrew, zigzag and barcode hairs) [1,3]</td>
<td>Painful lesions; microbiological test are useful [1,3]</td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
<td>Erythematous patches, scaling, follicular plugging and arborizing vessels; hyperpigmentation, white areas, atrophy and scarring alopecia in later phases [1,3]</td>
<td>Direct immunofluorescence shows immunoglobulin and complement deposition on skin sample (positive lupus band test).</td>
</tr>
<tr>
<td>Folliculitis decalvans</td>
<td>Hair tufting, follicular pustules, scarring alopecia [1,3]</td>
<td>/</td>
</tr>
<tr>
<td>Neutrophilic dermatoses such as sub-corneal pustular dermatosis</td>
<td>Flaccid pustules and vesicles, erosions [3]</td>
<td>Usual localization is trunk and main folds, scalp is rarely involved [3]</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>No specific dermoscopic features; clinically ulcer with undermined borders [1,3]</td>
<td>Painful lesions; histopathology can show neutrophilic infiltrate; scalp localization is infrequent [1,3]</td>
</tr>
</tbody>
</table>
References

Isolated Patchy Heterochromia With Pili Annulati Features on Light and Electron Microscopy

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Key words: hair heterochromia, pili annulati, microscopy

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Introduction

Isolated patchy heterochromia is a rarely described distribution of hair scalp mosaicism, where 2 distinct hair colors are present in the same person. We present the case of a patient with light microscopy and transmission electron microscopy (TEM) features that corresponded to pili annulati.

Case Presentation

A 12-year-old boy presented with a band of red hair over the interparietal region that was present since birth and had become more obvious over the years (Figure 1A). The rest of his scalp hair, eyebrows and eyelashes were brown. No previous traumas on the area, no treatments neither scalp inflammation were reported. The underlying scalp was normal. He had no diseases and the rest of physical exploration revealed no alterations. Light microscopy of both the red hair and brown hair showed light and dark segments under reflected light (Figure 1B). The latter corresponded to areas of cavitation within the hair cortex which after exposure to a 10% potassium hydroxide solution, induced disappearance of the dark areas within 5 minutes (Figure 1C). In order to perform TEM, the hair samples were mounted on stubs and sputter coated with gold palladium. TEM of the hairs shafts showed a circular to oval cross-section. The cuticle consisted of a cobblestone pattern with overlapping cells. The microfibers composing the cortex of the red hair shafts presented large gaps between them (Figure 1D). The clinical findings could correspond to isolated patchy heterochromia with pili annulati microscopic features.

Conclusions

Heterochromia of the hair represents a variant of pigmen
tary mosaicism that can present in different distributions (patchy, segmental, diffuse or blaschkoid). First described in 2001 by Restano et al, isolated patchy heterochromia has been rarely reported, with less than 25 cases in the literature [1-3]. It is usually a benign condition not related to any
genetic abnormalities of melanocyte migration (piebaldism, Waardenburg syndrome, Tietze syndrome, Vogt-Koyanagi-Harada syndrome), genetic diseases affecting pigmentation (tuberous sclerosis), inflammatory conditions damaging the melanocyte (vitiligo, halo nevus, regrowth in alopecia areata, herpes zoster, radiation), tumors (congenital melanocytic nevus), metabolic/nutritional defects (severe iron deficiency, vitamin B12 deficiency, kwashiorkor, phenylketonuria, Menkes syndrome), drugs (diazoxide, minoxidil, or chloroquine) or accidental causes (copper; green hair, cobalt; white-blue hair, trinitrotoluene; reddish-brown hair) [2]. No structural abnormalities of the hair shaft are detected at light microscopy or transmission/scanning electron microscopy but for a smaller diameter of the lighter hairs when compared with the darker ones [1].

Pili annulati represents a hair abnormality of uncertain origin that is usually inherited in an autosomal dominant pattern [4]. It is characterized by alternating light and dark bands that can be seen with the naked eye, resulting in a speckled appearance to the hair [5]. As in our case, the light bands correspond to air-filled cavities located within the cortex of the hair shaft. Altered hair growth and fragility are not clinical features in this condition [5].

In conclusion, we report the first case of isolated patchy heterochromia with pili annulati microscopic changes on light microscopy and TEM. These explorations should be routinely practiced to get a better characterization of hair heterochromia.

References

Application of Machine Learning Technologies to Improve the Diagnostic Value of Dermatoscopy, Combined with Digital Photo-fixation of Skin Neoplasms

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Key words: dermatoscopy, machine learning, skin neoplasms


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Introduction

Many of us who use the phone camera in professional practice have repeatedly encountered a situation where the visible image differs from the image obtained through the eyepiece of the dermatoscope.

I would like to bring to your attention in order to compare several clinical cases that have been refined in the Pixelmator Pro program with the ML Enhance tool. It is based on the use of machine learning technology to achieve the highest quality presentation of photographic material.

Case Presentation

Patient A (56 years old) has an area of redness with scaling on the surface in the area of projection of the left chin bone (Figure 1A). The picture is typical for actinic keratosis Grade 2 (AK) [1]. The symptom of "strawberry" is present, there are isolated areas of doubtful delicate pigmentation, the vessels are not clearly visualized (Figure 1B). In the same photo after improving the image with ML Enhance there are clearly visible pigment deposits that limit the follicular openings, a pronounced symptom of "strawberry", linear slightly branched vessels are traced over a longer period including outside the visual boundaries of the formation (Figure 1C). Photo processing optimizes the picture of pigmented AK. The extent of the lesion is slightly larger (1-2 mm), and the accumulation of melanin imposes certain restrictions on the use of photodynamic therapy as a treatment option.

Patient B (62 years old) has a papular element in the forehead on the right, dark in color, with keratin masses and peeling in the center (Figure 2A). During dermatoscopy,
the obtained image shows different sizes of blue and purple globules, single linear blood vessels in the thickness of the formation, and weak erythema of the surrounding tissues. The center is occupied by dark horny masses, there is a radiance that becomes lighter to the periphery (Figure 2B). This tends to consider this formation as a pigmented form of nodular basal cell carcinoma [2]. After photo processing, the deep occurrence of melanocyte structures of gray-blue color, multiple sparsely branched blood vessels, larger in the center and smaller - to the periphery of the formation, interspersed with white and radial lines, is clearly visualized. The visual size of the formation expands after photo processing mainly due to perifocal erythema. Such changes are more typical of nodular melanoma. Surgical excision was performed and the diagnosis of melanoma was confirmed.

**Conclusions**

Judging by the presented photos, the use of digital filters based on machine learning technology, in particular ML Enhance from the Pixelmator Pro package, in certain situations allows the dermatologist to improve the visualization of
changes in vascular pattern elements and pigment structures, which, in turn, facilitates the work of the doctor.

I would like to note that the use of the above tool in no way leads to the emergence of new elements of the dermoscopic picture. All of them are available for control during direct inspection through the eyepiece of the device, but are lost during photofixation, and become inaccessible during dynamic observation.

References


Clinicopathological and Demographic Characteristics of Paget’s Disease: a 4-year Study Showing a Male Predominance in Extra-mammary Paget

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Key words: paget, extramammary paget, mammary paget, Paget cells

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Introduction

Paget disease is a rare skin neoplasm and is categorized into mammary (MPD) and extra-mammary (EMPD) [1,2]. To date, its detailed histopathological features along with patients demographic characteristics have not been investigated in Iran. In this study, we performed a clinic-pathological analysis of Paget cases in a single tertiary center between 2016 and 2020.

Cases Presentation

A total of 32 cases including 26 (81.25%) females and 6 (18.75%) males with the mean age of 53 ± 9.96 years (range 34-78) were included in our study. All patients gave informed consent for participating in our study. The majority of our patients 26/32 (81.25%) had MPD, and 6/32 (18.75%) had EMPD. All cases had a history of scaly and erythematous prolonged lesions. Out of the 26 MPD cases, 25/26 (96.1%) were female and 1/26 (3.9%) were male. The mean age of the MPD cases was 51.03 ± 8.80 (range 34-78). Out of the 6 EMPD cases, 5/6 (83.3%) were male and 1/6 (16.7%) were female. The mean age of the EMPD cases was 61.5 ± 10.98 (range 42-74). Of note, all EMPD patients had ano-genital involvement. 2/6 (33.33%) cases had scrotum EMPD, 1/6 (16.66%) patient had penis and scrotum EMPD, 2/6 (33.3%) had peri-anal involvements, and
1/6 (16.66%) patient had labia major EMPD. Histopathological examination revealed the presence of cells with pale cytoplasm in addition to prominent nuclei along with a high nuclei cytoplasm ratio (N/C) in all 32 cases. Moreover, 10/32 (31.25%) had lymphocyte infiltration. IHC was performed for 6 EMPD patients and all of them were positive for CK7 and (CK AE3/AE1) (Table 1).

Conclusions

It is believed that Paget disease is more prevalent among older female patients [1-5]. The peak incidence of MPD is reported after the age of 60, while the mean age of the MPD patients in our study was 51 years [1].

Asian studies have shown a significant EMPD predominance in males and likewise, in our study, we found that the majority of EMPD patients were men, although, other studies have reported a higher prevalence of EMPD in female patients [1]. The most common location for EMPD is the vulva in 65% of cases, perianal area, scrotum, penis, and axilla [1]. In this regard, the only female EMPD patient in our study had labia major involvement. Based on the Ghazawi et al study, the most common sites for EMPD in males are the scrotum and penis, which is consistent with the findings of our study [4].

The histologic hallmark of Paget disease is the presence of Paget's cells [1]. In our study, the pathologic examination revealed the presence of Paget cells in all cases along with lymphocytic infiltrations in one-third of patients. In a study done by Elbendary et al the histopathologic evaluation showed no significant differences between MPD and EMPD which is consistent with our study [5].

Our study confirms that MPD is more prevalent than EMPD. Based on our study, there is a female predominance in MPD cases at younger ages in comparison to other reports, and penis and scrotal involvements of EMPD are highly probable locations.

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References

Not All Polarized-light Dermatoscopes May Display Diagnostically Critical Polarizing-specific Features

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Key words: dermoscopy, dermatoscopy, shiny white structures, polarizing-specific white lines

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Introduction

Since the introduction of polarized-light dermatoscopes it has become evident that there are some fundamental differences in image characteristics, in comparison to those provided by non-polarized dermatoscopy [1].

Non-polarized dermatoscopy provides color rendition without dilution of colors such as gray and blue by polarizing filters, and it provides a clear display of white clods and dots (milia-like cysts) in seborrheic keratoses [1-3].

Polarized dermatoscopy on the other hand displays features not seen in non-polarized dermatoscopy, including shiny white structures/streaks [4] (defined as short, bright, white lines distributed in a parallel or orthogonal orientation, which can only be seen with polarized dermatoscopy), four-dot clods (rosettes) and polarizing-specific structureless areas [4].

Each of these polarizing-specific features are known to have diagnostic relevance, but notably, it has been shown that shiny white structures/streaks can be critical in the diagnosis of melanoma [5] and in a meta-analysis they have been shown to have the equal highest odds ratio (OR) of 6.7 for the diagnosis of melanoma, compared to pseudopods (equal), irregular pigmentation (OR 6.4), blue-white veil (OR 6.3) and peppering (OR 6.3) [4].
Case Presentation

A 69-year-old woman with Fitzpatrick phototype-2 skin presented with a pigmented skin lesion on the ankle. Dermatoscopic examination with six different dermatoscopes revealed a chaotic pattern with clues to malignancy including white lines in non-polarized mode with all dermatoscopes, as well as shiny white lines/streaks in polarized mode with five dermatoscopes (Figures 1 and 2). Dermatopathology confirmed superficial spreading melanoma in situ.

Prior to biopsy, multiple images were taken with the six dermatoscopes coupled with 2 different camera devices. Because polarizing-specific features can be angle-dependent, for image acquisition each dermatoscope was rotated each time it was used in polarizing mode to produce the greatest display of shiny white structures/streaks possible.

Five dermatoscopes: Heine DELTA 20T, and Heine DELTAOne (Heine Optotechnik GmbH & Co. KG), DermLite DL4 (3Gen, Inc.), Opticlar (Albert Waeschle Ltd) and Illuco IDS 1100 (Illuco Co. Ltd.) displayed shiny white structures/streaks in polarized mode, with some apparent variations in intensity, distinctly different from the same device in non-polarized mode. The Heine DELTA 30 (Heine Optotechnik GmbH & Co. KG) did not display shiny white structures/streaks in polarized mode, the images being essentially the same as produced in non-polarized mode (Figures 1 and 2).

Figures 1-2 are labelled to display collages of polarized and non-polarized dermatoscopic images acquired with an iPhone 6 (Figure 1) and a Nikon Coolpix 4500 (Figure 2). No image manipulation has been performed other than cropping.

The authors all assert that the features demonstrated with respect to the Heine DELTA 30 are consistent with those observed by each of them in clinical practice.

Conclusions

Clinicians are invited to independently test these findings, as it is important for dermatoscopists to be cognizant of the characteristics of the instruments they use due to potential impact on diagnostic performance.

Acknowledgement

We acknowledge Dr Mohammadreza Rahimpour whose original observations in 2020 initiated this assessment.

Figure 1. Polarized and non-polarized images of a superficial spreading melanoma in situ, acquired with 6 different dermatoscopes coupled with an iPhone 6 camera. All photographs were taken by the same photographer (author CW) and are displayed without manipulation other than cropping.
References


Introduction

COVID-19 vaccination has been rapidly implemented worldwide, especially among patients with cancer. Local reactions with ipsilateral lymphadenopathy are among the most common side effects. A few cases of false-positive 18-fluorodeoxyglucose (18FDG) PET/computed tomography (CT) scan after COVID-19 vaccination have been reported [1,2]. This is especially important in oncologic patients, such as in cutaneous melanoma, where these findings might pose difficulties during their follow-up and management.

Case presentation

A 47-year-old male with BRAF mutant melanoma of the back and right axillary adenopathies underwent wide excision and lymphadenectomy and started adjuvant treatment with nivolumab. One month later, he presented disease relapse with satellitosis and a contralateral adenopathy in the left axilla, the latter detected by PET-CT. Treatment was changed to targeted therapy (dabrafenib and trametinib), reaching complete remission. An FDG-PET/CT from February 2021 showed no active disease. In May 2021, after eight months of targeted therapy, a
routine FDG-PET/CT showed substantial $^{18}$F-FDG avidity in the left axilla, with multiple malignant-appearing lymph nodes; no other foci were identified (Figure 1A). Given this finding, up to two ultrasound-guided biopsies were performed on the left axilla, describing at least one clearly malignant-appearing adenopathy in the ultrasound examination (Figure 1, B and C), and showing histologically lymphoid hyperplasia with no evidence of microscopic disease. Further questioning of the patient revealed that he had received the second dose of the COVID-19 mRNA vaccine (Moderna) in the left deltoid muscle 5 days prior to the routine PET/CT scan. Finally, a new PET/CT was performed 4 months later and revealed complete resolution of the hypermetabolic left axillary nodes (Figure 2), suggesting the diagnosis of reactive lymphadenopathy due to COVID-19 vaccine.

**Figure 1.** Imaging tests performed in May 2021. (A-D) Routine $^{18}$F-FDG-PET/TC: hypermetabolic lymphadenopathy in the left axillary region, the largest and with most metabolism of 13 mm (SUVmax: 3.9), suggestive of malignancy. (E) Sonographic exam of the left axilla after PET/CT findings: left axillary lymphadenopathy of rounded morphology with displacement of the central fatty hilum at the expense of great hypoechoic cortical thickening, sonographically suspicious. Core needle biopsy was taken from it.

**Figure 2.** (A-D) 4-month control $^{18}$F-FDG-PET/TC, September 2021: normalization of hypermetabolic lymphadenopathies in the left axillary region: resolution of the pathologic nodal uptake.
Discussion

Transient FDG uptake in normal or enlarged lymph nodes (mainly axillary, supraclavicular and cervical nodes) has already been described after administration of several types of vaccines [3,4]. This issue has also been observed now with the COVID-19 vaccination [1,2], being more frequently seen in patients vaccinated with Moderna, compared to Pfizer-BioNTech (72% versus 43%), and more intensely after the booster administration. Furthermore, it has been most frequently seen on day 1–7 after vaccination (71% of patients) and showed a negative correlation with time after vaccination [2].

This FDG avid axillary lymphadenopathy may confound interpretation in oncologic patients and change patient management (eg excessive follow-up imaging studies, unnecessary biopsies, treatment delays), besides causing additional patient anxiety [2]. This is the case of cutaneous melanoma, where misinterpretation in tumor staging or disease response during treatment may lead to deeply important differences in terms of disease prognosis and treatment algorithm.

In order to avoid misinterpretation, it is therefore important in oncologic patients to perform vaccination contralateral to the tumor expected nodal drainage, to ask patients about recent vaccination, and to perform FDG PET/CT before or at least 2 weeks after (optimally 4–6 weeks after) vaccine administration, if possible [2,4,5].

Conclusions

As COVID-19 vaccination has been rapidly implemented worldwide, clinicians should be aware of the transient appearance of hypermetabolic regional lymph nodes after its injection. Keeping this etiology in mind and following some recommendations for scheduling the PET-CT is especially important when evaluating oncologic patients to avoid misinterpretation.

References

Unilateral Rosacea in a Patient With Multiple Sclerosis

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Introduction

Rosacea is a common and chronic inflammatory skin condition of clinical heterogeneity and intriguing pathophysiological mechanisms. Herein, we report a case of unilateral rosacea in a patient with multiple sclerosis.

Case presentation

A 37-year-old woman presented to the dermatology department with a 2-year history of facial unilateral redness and paroxysmal pain. Over the last 2 years, she received multiple treatments, such as ivermectin cream, doxycycline and metronidazole gel, without any benefit. Her facial dermatosis presented as unilateral persistent erythema with multiple papules and pustules strictly confined to the right side (Figure 1). The skin biopsy revealed a perivascular and perifollicular inflammatory infiltrate consisting of lymphocytes, neutrophils with the presence of demodex mites, compatible with rosacea. The unilateral distribution of the dermatosis was suggestive of pre-existing neurological lesion. We referred the patient for additional testing, including an MRI of the brain, which demonstrated a demyelinating plaque at the trigeminal root entry zone consistent with trigeminal neuralgia secondary to multiple sclerosis (Figure 2). She was put on natalizumab and bolus steroid therapy. The pain has decreased. However, the rosacea got worse, probably because of corticosteroids.

Conclusion

Despite its high prevalence, the underlying pathophysiology of rosacea remains unclear. This observation highlights the complexity of the disease contributing mechanisms. Indeed, it describes a distinct variant of the disease denominated neurogenic rosacea, presented with unilateral arrangement and associated with an autoimmune disease. The pathophysiological mechanisms implicated in the development of
rosacea include dysregulation of the innate immune system, imbalance of commensal skin microbiota, and abnormal neurovascular signaling [1]. Neurogenic rosacea, a recently described rosacea subtype, demonstrates the role of local neural-associated mediators dysregulation in the pathophysiology of the dermatosis [2]. Moreover, it occurs more often in patients with neurological or neuropsychiatric conditions, including complex regional pain syndrome, essential tremor, depression and obsessive-compulsive disorder [2]. Dysesthesia secondary to neuronal injury was commonly reported and was associated with classical rosacea signs [2]. It is well known that patients suffering from rosacea have an increased of developing a number of auto-immune diseases, including multiple sclerosis. Yet, it is also important to notice that trigeminal neuralgia, attributed to multiple sclerosis, may explain the neurogenic inflammation leading to such skin condition as well as the unilateral arrangement of the lesions. Our case may also reflect a regional destabilization of the neuroimmunocutaneous system induced by multiple sclerosis. This hypothesis fully represents the concept of immuno-compromised district (ICD) [3,4]. ICD, a newly introduced pathogenic concept, stipulates that several different factors are likely to create a privileged cutaneous district, which explains the segmental presentation of many skin disorders, including bullous pemphigoid, pemphigus, lichen planus, discoid lupus erythematosus, drug eruptions and acne [4-6]. Trigeminal neuralgia attributed to multiple sclerosis, in analogy with the aforementioned facial nerve palsy, could locally alter the immune response and induce the occurrence of rosacea following the neurologically impaired facial side.

Regardless of the etiopathogenic mechanisms of rosacea, the interaction between the skin and the immune and nervous systems is currently well established, with rosacea being one of the established examples involving these various systems. The systematized arrangement of a dermatosis that is strictly confined to a specific area may refer to
the “immunocompromised district” concept, and thus promoting investigations into possible immunocompromising factors. Further research is clearly needed to better describe the underlying patho-physiologic characteristics and to identify additional effective treatment methods”.

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References

Dermoscopic Changes in Nevi During an Atopic Dermatitis Flare-up

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Case presentation

A 34-year-old male with a personal history of atopic eczema attended his annual digital dermoscopic control with a three-week flare-up of atopic dermatitis. On examination, he had scaly erythematous and eczematous plaques at the back and the flanks. Comparing the dermoscopic images we observed a global attenuation of the reticular pattern, even close to disappearance in some areas, and a pink-reddish coloration background in several nevi (Figure 1). We appreciated these changes in nevi located in areas affected with the atopic dermatitis flare-up but also in nevi in healthy skin.

Teaching point

The Meyerson phenomenon consists of an eczematous halo surrounding a melanocytic lesion [1]. The dermoscopic features in this phenomenon have been reported as the pigmented pattern - reticular and/or globular - encircled by dotted vessels associated with crust, without changes in the dermoscopic features of the involved melanocytic lesions [2]. However, in our patient the dermoscopic changes affected all the surface of the nevi and not all of them had clinical eczema. These changes are not consistent with previous descriptions of the Meyerson nevi.

It is known that in the reticular pattern, the pigmented lines correlate with the inter-papillar ridges and the holes of the network correspond to the dermal papillae. Thus, these dermoscopic findings may be explained by the histopathologic changes found in atopic dermatitis. Acute lesions of dermatitis show epidermal spongiosis and a perivascular infiltrate around vessels in the papillary dermis. These changes may be responsible for the attenuation of the reticular pattern and the pink-reddish background coloration.
References


Figure 1. Three examples of the dermoscopic findings in nevi before (A, C, E) and during (B, D, F) the atopic dermatitis episode.
Lichenoid Keratosis Simulating Melanoma: a Case Report

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Case presentation

An 80-year-old male was referred to the Dermatology Department for a pigmented lesion on his right arm that had been present for over twenty years but had rapidly grown and become more pigmented in the last three months. Physical examination showed a 10 mm dark, bluish-brown plaque and dermoscopy revealed a multicomponent pattern with multiple colors and pseudopods (Figure 1B). Reflectance confocal microscopy was performed, and the most prominent findings were a regular epidermal architecture, remnants of cord-like pattern in the dermoepidermal junction, and abundant aggregates of plump-bright cells in the papillary dermis, corresponding to melanophages (Figure 1C). An excisional biopsy was performed, and histopathological analysis showed epidermal hyperplasia with hyperkeratosis, vacuolar-interface dermatitis, and a dense dermal infiltrate of melanophages and lymphocytes. SOX10 stain highlighted dermal melanophage-aggregates (Figure 1, D and E).

Therefore, both confocal microscopy and histopathology were compatible with lichen planus-like keratosis (LPLK).

Teaching point

The diagnosis of seborrheic keratosis is typically straightforward. However, in cases of regression, also known as LPLK, these lesions may mimic melanoma or other malignancies [1]. Dermoscopic findings of lichenoid keratosis change as regression progresses, and several patterns have been described, such as light-brown or gray pseudo-networks, annular-granular structures and blue-gray globules [2]. We present a case in which some of those features were present, but were accompanied by other structures than have not been described yet in LPLK and that can be very misleading, such as pseudopods and blue-gray veil. Confocal microscopy was particularly useful in this challenging case, and diagnosis was confirmed by histopathology.
2 Figure 1. (A) Physical examination showed a 10 mm bluish-brown plaque. (B) Dermoscopy revealed a multicomponent pattern with multiple colors, and asymmetrically distributed blue-gray globules. Moreover, diffuse peripheral projections coalescing into pseudopods were observed on the left bottom side, and blue-gray veil and annular-granular structures in the center. (C) Reflectance confocal microscopy showed remnants of cord-like pattern, and aggregates of small-bright particles in the papillary dermis, corresponding to melanophages. (D) Histopathology, H&E 200x. Epidermal hyperplasia with hyperkeratosis, vacuolar-interface dermatitis and a dense dermal infiltrate of melanophages and lymphocytes. (E) SOX10 (Sry-related HMg-Box gene 10), 400x. Absence of melanocytic hyperplasia, and dermal melanophage-aggregates can be observed.

References


Necrobiotic Xanthogranuloma as Sign of Monoclonal Gammopathy

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Case presentation

A 52-year-old woman referred to our skin cancer unit for the presence of yellow periorbital plaques that enlarged over the past decade. Based on the clinical and dermoscopic presentations (Figure 1), a clinical diagnosis of necrobiotic xanthogranuloma (NX) was suspected. A full laboratory workup was performed including skin and bone marrow biopsy, CT scan of the orbital region and urine examination. Tests revealed an IgG paraproteinemia without bone involvement and, based on skin biopsy, the diagnosis of NX BRAF wild type was confirmed.

Figure 1. (A) Clinical appearance of necrobiotic xanthogranuloma showing eyelid and periorbital yellow plaques. (B) Dermoscopic features of XN showing yellow structureless areas that correspond to the presence of histiocytes in the dermis. (C) H&E histological detail showing foamy histiocytes in the dermis.
Teaching Point

Necrobiotic xanthogranuloma is a rare manifestation of non-Langerhans histiocytosis and it is often associated with monoclonal gammopathy.

References

Atypical Spitz Nevus: Dermoscopic, Confocal Microscopic and Histopathological Correlation

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Case presentation

A 12-year-old girl was observed for a new asymmetric pink and black papule on her back. Dermoscopy revealed a multicomponent pattern with pink pigmentation, and blue-white veil. By reflectance confocal microscopy (RCM) overall asymmetry was noted. Irregular honeycomb pattern of the epidermis and compact dermal nests, matching the pink pigmentation area were evident while, in the blue-white veil dermoscopic area, multiple superficial dendritic cells and an irregular meshwork pattern at the dermal-epidermal junction were seen. Considering these findings, surgical excision was performed. Histopathological examination disclosed an asymmetric compound proliferation of melanocytic epithelioid cells. Its junctional element was predominantly nested, whereas the dermal aspect was highly cellular with fascicles of slightly pleomorphic epithelioid cells throughout the entire dermis. These findings favored the diagnosis of atypical Spitz nevus.

Teaching point

Atypical Spitz nevi represent an intermediate category of melanocytic lesions whose differentiation from melanoma is difficult because of overlapping features [1]. RCM represents a noninvasive diagnostic add-on, but RCM features of atypical Spitz tumors are not well characterized [1,2].

Confocal features that may help to differentiate Spitz nevi from melanoma have already been identified [2]; however, a study from Guida et al stated that RCM was not useful in lesions with multicomponent or unspecific dermoscopic patterns since many “malignant” features were shared between both entities [1]. We are able to overcome this gap if we consider the patient age when evaluating a spitzoid lesion. Besides that, this case illustrates the RCM features of an atypical Spitz nevus with an impressive dermoscopic and histopathological correlation.
Figure 1. Spitz nevus. (A) Clinical picture: asymmetric 1cm diameter papule with uneven pink and black color. (B) Dermoscopy picture: multicomponent pattern with irregular brown and pink pigmentation, and blue-white veil. (C) Confocal microscopy picture: C1 - epidermal honeycombed structures and thin dermal papillae; C2 - irregular meshwork pattern at the dermal-epidermal junction and associated areas of totally disarranged papillary contours owing to multiple bright fusiform cells with dendrites (white asterisks). (D) Histopathological pictures: D1 - Overall asymmetric polypoid-like melanocytic compound proliferation with an important deep component. The junctional element of the lesion is predominantly nested while the dermal aspect is highly cellular (white asterisk) (H&E, x25). D2 - Higher magnification showing the cellular dermal component of slightly pleomorphic epithelioid cells organized in fascicles. These cells immunostaining for HMB-45 was positive throughout the entire dermis (H&E, x100).

References


Aneurysmal Dermatofibroma After Varicose Vein Surgery

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Case presentation

A 45-year-old man was referred to dermatology consultations for evaluation of a pigmented lesion on the left leg. The lesion appeared at the incision site of a varicose vein surgery performed one year prior.

Clinical examination revealed an indurated 12 mm brown plaque (Figure 1A). Dermoscopy showed at the center white network surrounded by bluish areas and a rainbow pattern, and at the periphery a homogeneous brown color (Figure 1B). Histopathological examination revealed blood-filled spaces with peripheral hemosiderin deposits, and a dense collagenous stroma containing spindle cells (Figure 1C). Immunohistochemical tinctions for Factor XIIIa (Figure 1D) and for CD68 were positive, while human herpesvirus 8 was not detected.

Teaching point

Aneurysmatic dermatofibroma represents approximately 1.7% of all types of dermatofibromas [1]. Like any dermatofibroma, this subtype may appear after local trauma. Its clinical diagnosis can be difficult due to its resemblance to malignant tumors, such as Kaposi sarcoma, angiomatoid malignant fibrous histiocytoma and melanoma [2].
References


Figure 1. (A) Clinical examination of the lower limbs. The hematoma on the right leg is unrelated to the reason for consultation. (B) Multi-component dermoscopic pattern composed of central white stripes with rainbow areas, and a peripheral brown network. (C) Dense tumoral stroma with congested blood vessels; the epidermis shows basal layer hyperpigmentation, acanthosis and hyperkeratosis. (D) Diffuse positivity for factor XIIIa throughout the tumor.
Dermoscopical Findings of the Evolving Pigmented Spitz Nevus in a Child

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Case presentation

A 12-year-old girl presented for a routine examination with a 4-mm oval-shaped dark brown papule on the right temple which slowly grew since her early childhood (Figure 1A). Dermoscopy showed a homogenous half-blue and half-brown presentation (Figure 1B 20x, FotoFinder GmbH). The lesion has changed subtly within two years (Figure 1C). After three years, the lesion displayed a uniform blue-brown color with streaks distributed at the periphery (Figure 1D). The high magnification dermoscopy revealed peripherally distributed brown roundish cells [1] (Figure 1E, F, 400x, FotoFinder GmbH). The patient underwent excision of the lesion and histopathological diagnosis of Spitz nevus was established. The consent to publish data has been obtained from the patient’s parents.

Teaching point

Typical for children Spitz nevi usually occur as a solitary, rapidly growing, pink nodule on the face [2]. This case represents a less common presentation of Spitz nevus in childhood, with changes extremely extended in time.

References


Figure 1. (A) The clinical presentation of the nevus - a 4-mm oval-shaped dark brown papule. (B) Dermoscopic image of the nevus at the first visit with a homogenous half-blue and half-brown presentation. (C) Subtle changes in dermoscopic features of the nevus after two years, with streaks appearing in the upper left quadrant (claret asterisks). (D) Dermoscopic image of the nevus after three years with uniform blue-brown color with streaks distributed at the periphery (green asterisks). (E and F) High magnification dermoscopic image of the lesion revealed blue-grey background with distinctive brown oval structures corresponding to the hair follicles (blue arrows) and peripherally distributed brown roundish cells corresponding to peripheral streaks (red arrows).
Subungual Eccrine Angiomatous Hamartoma: Description of a Novel Dermoscopic Feature

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Case presentation

A 45-year-old woman presented with a 2-month history of progressive tenderness at the tip of the left first toenail. Clinical examination showed no gross abnormalities within and beneath the nail plate. Nail plate dermoscopy revealed longitudinal yellowish-brown to yellowish-red areas with no remarkable changes in the nail plate, lunula, or proximal nail fold (Figure 1A). Histologic examination showed increased number of eccrine glands with irregular, dilated blood vessels (Figures 1, B and C), consistent with the diagnosis of eccrine angiomatous hamartoma (EAH).

Teaching Point

EAH is a rare, benign combined eccrine and vascular malformation located mainly on the limbs, rarely in subungual areas. To our knowledge, this is the first report on nail plate dermoscopic descriptions of EAH. The presence of yellowish-brown to yellowish-red areas may reflect the
Figure 1. (A) Nail plate dermoscopy revealed yellowish-brown to yellowish-red areas, which are arrayed longitudinally under the nail plate. (B, C) Histopathology showed the hamartomatous presentation of the lobules of the eccrine glands accompanied by abnormally dilated vessels. (H&E stain; original magnification: B, ×4; C, ×20.)

numerous dilated eccrine glands and clusters of dilated capillaries among and around the eccrine glands, which could be helpful in its diagnosis [1,2].

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References


Cobblestone-like Skin

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Case presentation

A 55-year-old Caucasian man who was positive for obesity, hypertension and congestive heart failure presented for a sixteen-months history of recurrent lower limbs swelling with progressive thickening of the skin. Clinical examination revealed lymphedema with deformed fibrotic enlargement of the extremities. Brownish pigmentation, with generalized lichenification (Figure 1A) and cobblestone-like papules and nodules on the lower two thirds of both legs were also notable (Figure 1B). Swabs from some ulcerated lesions of the left pretibial area were obtained, but cultures did not show any pathogens growth. Histological examination of a nodular lesion showed hyperkeratosis, parakeratosis, and acanthosis of the epidermis, as well as edema and dilated lymphatic spaces in the papillary and reticular dermis. No neoplastic changes were found. Diagnosis of elephantiasis nostras verrucosa (ENV) was made upon clinical and histopathological findings.

Teaching point

ENV is an uncommon dermatological disorder characterized by hyperkeratotic, verrucous, and papillomatous projections [1]. Keong described it as “a non-filariasis chronic lymphedema, causing disfigurement of the extremities, and it will lead to recurrent infections and disabilities” [2]. The diagnosis is based on anamnesis and peculiar skin modifications [1]. Differential diagnosis includes venous stasis dermatitis, pretibial myxedema and filariasis [1]. Several therapeutic options have been described in literature such as skin care, weight reduction, compressive medications and physiotherapy [2]. Oral retinoids, surgery, and antimicrobials for super infections have also been used [1]. The unique target of the therapy is represented by restoring function and reducing physical disability. As chronic lymphedema could be the antechamber of lymphangiosarcoma, long-term follow-up is highly recommended [2].
Figure 1. (A) Lymphedema of the lower extremities, with brownish pigmentation and generalized thickening of the pretibial skin. (B) Close view of cobblestone-like papules and nodules on the lower two-thirds of left leg.

References


Erythema Multiforme: a Clinico-Dermoscopic-Histopathological Correlation of Evolving Targetoid Lesions

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Case presentation

A 32-year-old male was diagnosed with recurrent erythema multiforme secondary to orolabial herpes. Dermoscopy (polarised light, Dermlite DL4) of evolving targetoid lesions is shown in Figure 1.

Teaching point

The central ruptured vesicle is seen as a central circular yellowish-pink area on dermoscopy and correlates with subepidermal split on histopathology. The black pigmentation is seen as brown-black colored dots and clods on dermoscopy and correlates with necrotic keratinocytes along dermo-epidermal junction on histopathology. A well-defined urticaria-like erythematous plaque is seen on dermoscopy as structureless homogenous pink-white area obliterating the normal pigment network and correlates with papillary oedema on histopathology.

We discovered that, in the absence of treatment, the size of individual lesions increases as the time since the onset of the lesion increases. This is associated with dermoscopic feature of increase in the number and density of black-brown dots and clods, that we have termed as “splash of ink” appearance in fully evolved targetoid lesions, which could indicate ongoing damage to basal keratinocytes and melanocytes and thus disease activity. Dermoscopy can be used to determine the relative age of targetoid lesions. The size of the targetoid...
lesion and the size of “splash of ink” appearance indicates the evolution of the individual lesion. Targetoid lesions with the earliest onset will have largest size and “splash of ink” appearance and vice-versa. We believe that regardless of the cause of EM, its morphological appearance will be consistent in all cases, and treatment will result in fading of “splash of ink” appearance. However, further studies are needed to validate this.

References

White Rosettes as a New Dermoscopic Finding in Acute Cutaneous Lupus Erythematosus Patient With Unilateral Erythema

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Case presentation

A 65-year-old female presented with a 2-week history of swelling erythema (10 cm \times 8 cm) on her left cheek, without pruritus, pain, or systemic complaints (Figure 1A). Dermoscopy showed some whitish scales, mixed vascular pattern, and remarkable white rosettes on a pinkish reddish background (Figure 1B). Skin biopsy of the lesion revealed epidermal atrophy in addition to follicular plugging, obviously vacuolar degeneration of the basal layer, and remarkable superficial and deep perifollicular lymphocytic inflammatory infiltrate (Figure 1C). After treatment of 200 mg hydroxychloroquine daily, the lesion was relieved entirely in the eighth week. We have obtained informed consent from this patient.

Teaching Point

Acute cutaneous lupus erythematosus (ACLE) is a subcategory of LE-specific skin disease, which is usually diagnosed based on typical lesions. Because the ACLE has less cutaneous involvement, it is essential to identify such lesions early for appropriate interventions promptly. White rosettes are not lesion-specific and were reported in many lesions, including discoid lupus erythematosus (DLE) [1], while there are few reports of white rosettes in ACLE in the literature. In our case, lots of white rosettes with the same size, shape, and orientation angle are observed in the same field of view.
Figure 1. (A) Unilateral swelling erythematous patch on the patient’s left face without contralateral involvement. (B) Dermatoscopy of a target lesion (the site highlighted in (A)) shows some whitish scales, mixed vascular pattern (black triangle), and remarkable white rosettes (black circle) with some white shiny structures (black square) on a pinkish reddish background. (C) Histopathological of the skin biopsy showing follicular plug, superficial and deep perifollicular lymphocytic infiltrate (H&E×100). (D) Vacuolar degeneration of the basal layer and (E) Remarkable superficial and deep perivascular and periadnexal lymphocytic infiltrate at higher magnification from the sites highlighted in (C) respectively (H&E×200).

References

Dermoscopy of Diabetic Dermopathy

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Case presentation

A 43-year-old man presented with asymptomatic multiple, bilateral, small, brown macules on pretibial areas which had been present for the last 3 years (Figure 1A). The patient was diagnosed with type 2 diabetes 18 years ago, with associated retinopathy and nephropathy.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{(A) Clinical picture. (B) Dermoscopic image shows two central areas (inside blue dotted-line) surrounded by an ill-defined brown peripheral rim. (C) High magnification dermoscopic image. “Ring-like” globular structures can be identified in the brown peripheral rim (black arrows). Fine scarcely branching linear vessels (white arrows) are separated by blurred grayish-white streaks (\textdagger) which look like dusky Wickham striae.}
\end{figure}
Dermoscopic evaluation of the lesions revealed a distinctive pattern which was characterized by a one or multiple central area/s surrounded by an ill-defined brown peripheral rim (Figure 1B). “Ring-like” globular structures could be identified in the brown peripheral rim. Finally, central areas dermoscopically demonstrated several fine scarcely branching linear vessels separated by blurred greyish-white streaks which resembled dusky Wickham striae (Figure 1C).

The diagnosis of diabetic dermopathy was confirmed by histopathological assessment. These dermoscopic features show an excellent correlation with histologic findings [1,2]. Thus, the greyish-white color of the central area probably corresponds to increased collagen density and fibroblastic proliferation, and the fine branching vessels probably are telangiectasias in the papillary dermis underlying an atrophic epidermis. The brown peripheral rim can be explained by hemosiderin deposition in dermis and increased melanin of basal cells.

Teaching point

Dermoscopic features of diabetic dermopathy (as described above) are different from other diseases that can also present with pretibial pigmented patches, such as early lesions of necrobiosis lipoidica, pigmented purpuric dermatosis or lichen planus.

References

Yellow Urticaria

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Case presentation

A 51-year-old patient with metastatic colorectal cancer, treated with dabrafenib, trametinib and cetuximab, presented with the acute onset of yellowish skin lesions. On clinical examination, multiple itching, intense yellowish skin swellings on the trunk and extremities were observed. The unaffected skin, however, was not icteric, contrary to the sclerae (Figure 1 A-C). Besides marked leukocytosis and elevated liver function parameters (GGT 708 U/L, GOT 80 U/L, GPT 52 U/L) laboratory investigations revealed a markedly increased serum bilirubin level (9.55 mg/dl; 0.1-1.2). Our patient suffered from acute urticaria with wheals appearing yellowish due to marked elevated serum bilirubin. An association with the aforementioned drugs in our case is likely, but urticaria may also be induced by an inflammatory process in a patient suffering from cancer. The lesions resolved within a few days under antihistamine treatment, and the skin color of the previous prominent yellowish lesions adapted to that of the surrounding skin. Due to his underlying disease, the patient died a few weeks later.

Teaching point

Novel therapies like checkpoint-inhibitors or immunoncological agents revolutionized treatment in several advanced malignancies. Consequently, a broad spectrum of adverse events in different degrees of severity can occur at any time of therapy, even after cessation of treatment.

Urticaria is a very common skin disease; yellow urticaria, however, is a seldom and unusual variant and to date no more than ten cases are reported since the first report in 1969 and all hitherto reported cases have a hyperbilirubinemia as definitive cause in common [1,2].

References

Figure 1. (A) Clinical image showing the left arm with multiple yellowish skin swellings. (B) Close up. (C) Yellow-colored sclerae.
Recurrent Microinvasive Subungueal Squamous Cell Carcinoma in a HIV Patient: a Case of Good Response to Photodynamic Therapy

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Introduction

A 37-year-old male patient with a verrucous lesion affecting the second finger of the left hand, present for about 3 months. Medical history revealed HIV infection, Kaposi sarcoma, anal squamous cell carcinoma (SCC) and muco-cutaneous leishmaniasis. The diagnosis of microinvasive subungual SCC was made with a punch biopsy. The patient denied radical surgery and a conservative shaving was performed. Eight months later, the lesion relapsed (Figure 1, A and B). The diagnosis of recurrent subungual SCC was made by pathology. An X-ray of the finger excluded a bone involvement.

Due to the patient decision of denying surgery, we decided to perform a cycle of 4 sessions of conventional photodynamic therapy (C-PDT), using methyl aminolevulinate (MAL) (METVIX® cream, Galderma Medical Solutions) under occlusion for three hours. The lesion was irradiated by a red light-emitting diode lamp (Aktilite CL128®, Galderma, wavelength 630 nm), at 80 mW/cm² for 12 minutes. The procedure was repeated 4 times at one-week intervals. After the first step we observed a partial improvement (Figure 1, C and D). After the fourth C-PDT step, the lesion had almost completely disappeared (Figure 1, E and F). The patient did not relapse 6 months after last C-PDT session.
Figure 1. (A) Clinical presentation of recurrent subungual squamous cell carcinoma (SCC) on the second finger of the left hand. (B) Dermoscopy of the verrucous lesion, with hyperkeratosis and dotted vessels. (C) Recurrent subungual SCC after the first step of conventional photodynamic therapy (C-PDT). (D) Dermoscopy of the lesion after the first step of C-PDT. (E) Recurrent subungual SCC after the fourth step of C-PDT. (F) Dermoscopy of the lesion after the fourth step of C-PDT.
Teaching point

PDT is a safe, non-invasive therapy, with good cosmetic results, for several dermatologic conditions, such as actinic keratosis and superficial non-melanoma skin cancer [1-2]. We hypothesize that C-PDT may be a promising therapy for high-risk recurrence SCC, especially in acral sites, leading to a rapid healing process and being at the same time a well-tolerated, less painful procedure.

References