Pemphigus Vulgaris: Present and Future Therapeutic Strategies

Dario Didona¹, Giovanni Paolino², Giovanni Di Zено³, Biagio Didona³, Riccardo Pampena¹, Matteo Riccardo Di Nicola², Santo Raffaele Mercuri²

¹ Department of Dermatology and Allergology, Philipps University, Marburg, Germany
² Unit of Dermatology, IRCCS San Raffaele Hospital, Milan, Italy
³ IDI-IRCCS, Rome, Italy
⁴ Centro Oncologico ad Alta Tecnologia Diagnostica-Dermatologica, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Italy

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Corresponding author: Matteo Riccardo Di Nicola, Unit of Dermatology, IRCCS San Raffaele Hospital, Milan, Italy.
E-mail: dinicola.matteo@hsr.it

ABSTRACT

Pemphigus vulgaris (PV) belongs to the group of autoimmune blistering diseases. PV can affect not only mucous membranes, but also the skin and it is characterized by serum IgG autoantibodies against desmoglein 1 and 3, two major components of desmosomes. The introduction of glucocorticoids improved dramatically the prognosis of patients affected by PV. However, long-term use of high dose corticosteroids and adjuvant steroid-sparing immunosuppressants can lead to several adverse events. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been recently approved as in-label therapy for PV, leading to an improvement of the prognosis and higher remission rate. Furthermore, other anti-B-cell therapies and several anti-CD20 biosimilars have been introduced in the clinical practice. We focused on present and future therapeutic approaches in PV.

Introduction

Pemphigus vulgaris (PV) belongs to autoimmune blistering diseases and it is characterized by flaccid blisters and erosions, that can involve not only the skin, but also mucous membranes [1]. Three main forms of pemphigus are described: PV, pemphigus foliaceus (PF), and paraneoplastic pemphigus [1–6].
Methods

We conducted a review to identify studies that documented the current therapeutic strategies for pemphigus vulgaris, as well as the future ones. All type of study, in English language, was considered eligible for this review, including case reports and case series. The main search was conducted in the electronic databases of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to January 2021 using different combinations of the following terms: “pemphigus”, “pemphigus vulgaris”, “treatment” and “therapy”. Additionally, we concluded the manual search by reviewing all relevant citations within the selected and identified articles.

Epidemiology

PV is the most frequent type of pemphigus [1]. It usually affects people between 50–60 years of age [7]. A female to male ratio of 5.0 was reported in the USA [7]. In the American general population, an annual incidence of 4.2/1,000,000 inhabitants was reported, but it was much higher in the Jewish-American population [7]. This is due to the most prominent expression of specific HLA class II genes in PV patients with Jewish background, such as HLA-DRB1*0402 and HLA-DQB1*0503 [7].

Clinical Features of PV

PV usually arises with painful and refractory oral erosions (Figure 1) [1]. Furthermore, other mucous membranes can be affected [1]. Most of patients also develop flaccid skin blisters that rapidly evolve into oozing erosions (Figure 2) [1]. Rarely, pemphigus patients show a clinical and serological transition from PV to PF or conversely. This phenomenon could be due to the epitope spreading, a process of diversification of B- or T-cell responses from the initial dominant epitope to a second one [8].

Pathogenesis

Cutaneous desmoglein-1 (Dsg1) can be expressed in the whole epidermis, cutaneous Dsg3 is typically found in the lower epidermis, while in the mucosa Dsg1 and Dsg3 are located in the whole squamous layer, with a higher expression of Dsg3 [9]. Therefore, PV patients who show only anti-Dsg1 immunoglobulin G (IgG) serum antibodies develop only skin blisters, and, in the case of detectable anti-Dsg3 IgG serum antibodies, the clinical phenotype is characterized by erosions or ulcerations of mucosal membranes [10]. Furthermore, the production of both anti-Dsg1 and anti-Dsg3 IgG serum autoantibodies provokes skin and mucosal lesions [10].

Evidence suggests that anti-Dsg1 and anti-Dsg3 autoantibodies are responsible for a loss of cell-cell adhesion between keratinocytes [11,12]. The most important targets for autoantibodies in PV are represented by the extracellular domains of Dsg [13,14]. Further mechanisms can also lead to acantholysis in PV, such as Dsg endocytosis and desmosome disassembly [15,16], and intercellular stretch at non-acantholytic cell layers caused by pathogenic autoantibodies [17,18]. In addition, non-Dsg IgG serum autoantibodies have been reported as important in PV pathogenesis, including those directed against desmocollins, mitochondria, pemphaxin, and alpha-9 acetylcholine receptor [13,19].

Diagnosis of PV

The diagnosis of PV requires not only compatible clinical features, but evidence of pathological features of involved skin and the presence of autoantibodies by direct immunofluorescence microscopy of non-affected skin. Indirect immunofluorescence microscopy, enzyme-linked immunosorbent assay and other techniques have a confirmatory role [5].

The most important pathological feature is the intraepidermal acantholysis [20]. Direct immunofluorescence of non-affected skin detects IgG and proteins of complement C3 (C3) on epidermal keratinocytes (Figure 3) [20,21]. Indirect
immunofluorescence on monkey esophagus detects a fishnet pattern due to IgG antibodies reactivity to cell membrane of epithelial or epidermal cells [20].

**Current Therapies**

**Corticosteroids**

Prednisolone is usually administered as initial therapy in PV in association with immunosuppressive agents, such as azathioprine (AZA) and mycophenolate mofetil (MMF), or anti-CD20 monoclonal antibodies [1]. In patients with several comorbidities and in those who cannot undergo a therapy with anti-CD20 monoclonal antibodies or immunosuppressive agents, prednisolone as monotherapy is still recommended as first-line therapy [1]. Nevertheless, plenty of side effects have been described after prolonged corticosteroid (CS) therapy, including severe infections, secondary impairment of adrenal glands, osteoporosis, hyperglycemia, and hypertension [1].

**AZA**

AZA downregulates purine metabolism, and blocks the synthesis of DNA, RNA, and proteins. In addition, AZA causes a reduction of Langerhans cells and monocytes, and reduces the activity of T- and B-lymphocytes [1]. Furthermore, AZA blocks T-helper-cell dependent responses of B-cells [1]. AZA dosage should be adapted to thiopurine-methyltransferase activity, the enzyme responsible for AZA metabolism. Adverse events (AEs) are reported in up to 30% of patients, including nausea, pancreatitis, diarrhea, aphthous stomatitis, and maculopapular rash [1]. Pancytopenia and hepatotoxicity are reported as severe AEs [1].

**MMF**

MMF leads to a suppression of the immune system by a selective blockade of inosine monophosphate dehydrogenase, that produces a downregulation of the pathway of purine synthesis in T- and B-cells [1]. Because of its mode of action, MMF represents a safer CS-sparing drug compared to other immunosuppressive drugs [1]. Moderate gastrointestinal AEs are frequently reported [1]. In addition, MMF can increase the risk of hematologic malignancies, skin basal cell, and squamous cell carcinoma [1].

**Cyclophosphamide**

Cyclophosphamide (CYP) is an alkylating prodrug [1]. It is converted in the liver into 2 active metabolites, which cause cell death through the downregulation of DNA replication. CYP blocks the release of cytokines and reduces the lymphocytic inflammation [1]. It is recommended as a rescue drug, since its administration is characterized by several AEs, such as nausea, fatigue, pancytopenia, and alopecia [1]. A severe complication of CYP treatment is hemorrhagic cystitis, which can be avoided with the administration of adequate fluid intake and sodium 2-mercaptoethane sulfonate [1]. CYP administration can cause transitional cell carcinoma of the bladder [1]. In addition, transient or lasting impairment of gonadal function has been reported [1].

**Rituximab**

Rituximab (RTX) is a chimeric monoclonal anti-CD20 antibody, that targets CD20, a transmembrane receptor, expressed at several stages of the B-cell maturation [22]. RTX causes B-cell depletion through different mechanisms: 1) direct induction of apoptosis; 2) complement-dependent cytotoxicity; 3) antibody-dependent cytotoxicity; 4) antibody-dependent phagocytosis; and 5) trogocytosis [23,24].

The last mechanism is characterized by the elimination of RTX-CD20 complexes by macrophages, that causes cell death by a still unknown mechanism [25].

PV patients on RTX can develop opportunistic infections, such as *Pneumocystis jirovecii* pneumonia [23], but it is still unclear whether PV on RTX may receive a *Pneumocystis jirovecii* prophylaxis [26]. Furthermore, reactivation of hepatitis B and C and tuberculosis could be possible [23]. Side effects related to RTX administration are represented mostly by type I allergic reaction and cytokine release syndrome [23]. Furthermore, late AEs include serum sickness and toxic epidermal necrolysis [23,27].

The optimal RTX dose in PV is still under debate. Two main protocols have been proposed: 2 intravenous infusions of 1000 mg each 2 weeks apart (rheumatoid arthritis protocol) and 4 infusions of 500-mg each weekly [23,28]. In 2017, a prospective randomized controlled trial that compared RTX combined with CS versus CS alone in patients with newly diagnosed PV showed a significantly higher remission rate off-therapy in the RTX cohort [29]. Furthermore, re-treatment with a single RTX dose of 500 mg after 12 and

**Figure 3.** Deposition of IgG and/or C3 on the surface of epidermal keratinocytes detected by direct immunofluorescence. C3 = proteins of complement C3; IgG = Immunoglobulin G.

18 months was highly effective in achieving a long-term clinical remission [29].

**Ofatumumab**

Ofatumumab is a fully human anti-CD20 monoclonal antibody used as therapy in chronic lymphocytic leukemia. Its target is represented by another CD20 epitope compared to the one targeted by RTX [30]. Ofatumumab has been used for PV patients who developed side effects or loss of response to RTX [31].

**Intravenous Immunoglobulin**

Intravenous immunoglobulin (IVIG) is used for immunomodulatory therapy of several inflammatory disorders [32]. The mechanism of action of IVIG is still not completely known, but several modes of action have been proposed [33,34]. However, the main mechanism of action is considered the implementation of degradation of immunoglobulins by binding the neonatal of Fc receptor (FcRn) [33,34]. The standard administration schedule is 2 g/kg in 5 days (400 mg/kg per day in 5 days) must be kept in mind that IVIG does not show an immunosuppressive activity [32,34]. It can be administered in combination with systemic CS and other immunosuppressants in recalcitrant PV [35].

Side effects were not frequently described [36,37]. Early AEs include headache, nausea, fever, tachycardia, malaise, arthralgia, and dyspnea [36,37]. Late-onset AEs include aseptic meningitis, acute renal failure, thromboembolic events, and pseudohyponatremia [36,37].

**Immunoadsorption**

Through immunoadsorption (IA) IgG were passively removed from systemic circulation [1]. The combination of IA with immunosuppressive therapies is considered an effective treatment for pemphigus patients with severe activity, because IA allows an immediate removal of pathogenic autoantibodies. Infections are still the most frequently complications [1]. IA is considered an effective treatment in patients with severe disease (> 30% of the body surface or >25% of genital or oral mucosa) or with involvement of the conjunctiva or esophagus [1].

**Future Therapeutic Approaches**

**CAR-T Cell Therapies**

Chimeric antigen receptor (CAR)-T-cell therapy has been described as promising therapy in hematology [1]. CAR-T cell therapy is a paradigmatic example of adoptive cell transfer therapy. Indeed, autologous T-cells are modified ex-vivo to express a CAR, which leads to a specific targeting of a particular antigen and elimination of the antigen-expressing cells [38,39].

The CARs are composed of 3 domains: 1) the extracellular domain, which represents the antigen recognition domain; 2) the transmembrane and hinge domain; 3) the one or more intracellular T-cell signaling domains [39]. In 2016, T-cells were modified to express a chimeric autoantibody receptor (CAAR), which was composed by Dsg 3 fused to a CD137-CD3-zeta signaling domains [39]. Desmoglein-3 CAAR-T-cells show a selective cytotoxicity directed to cells with anti-Dsg3 B cell receptors in vitro and destroy Dsg3-specific B-cells in vivo. In a PV mouse model, CAAR-T cells reduced pathogenic IgG antibodies and improved the clinical picture [40].

**Anti-Neonatal Fc Receptor (FcRn)**

The FcRn is formed by the MHC class I-like heavy chain and the β2-microglobulin light chain [41]. It has played a central role in the homeostasis of IgG. Indeed, the IgG-FcRn complex avoids the degradation of IgG, leading to a recycle and release of IgG [42,43]. In a Knockout Mouse for FcRn, loss of cell-cell adhesion by passive transfer of antibodies against Dsg was not evident [44]. Furthermore, it was reported that blocking FcRn impaired the capability of PV to determine acantholysis [45]. A randomized, double-blind, placebo-controlled study with efgartigimod, a human IgG1-derived Fc fragments bound to FcRn, reported the efficacy of the drug in reducing the IgG titer in up to 75% of patients [46].

**Conclusions**

PV remains a therapeutic challenge for clinicians. Several therapeutic options are currently available. However, finding a specific treatment for a particular patient is not easy. Therefore, knowledge and management of multiple therapeutic choices for patients with PV play a pivotal role in better patient management.

**References**


Clinical and Dermoscopic Approaches to Diagnosis of Frontal Fibrosing Alopecia: Results From a Multicenter Study of the International Dermoscopy Society

Michela Starace¹, Gloria Orlando², Matilde Iorizzo³, Aurora Alessandrini¹, Francesca Bruni¹, Victor Desmond Mandel⁴⁻⁵, Kelati Awatef⁶, Horacio Cabo⁷, Gabriella Fabbrocini¹³, Baybay Hanane⁸, Sven Lanssens⁹, Alejandro Lobato-Berezo¹⁰, Fatima Zahra Mernissi¹⁶, John Paoli¹¹⁻¹², Angela Patri¹³, Emilia Noemi Cohen Sabban⁷, Martyna Sławińska¹⁴, Michał Sobjanek¹⁴, Oscar Zaar¹¹⁻¹², Giovanni Pellacani⁴⁻¹⁵, Bianca Maria Piraccini¹

¹ Department of Experimental, Diagnostic, and Specialty Medicine-Division of Dermatology, University of Bologna, Bologna, Italy
² Department of Medicine - DIMED, Dermatology Unit, University of Padova, Italy
³ Private Dermatology Practice, Bellinzona, Lugano, Switzerland
⁴ Dermatology Unit, Surgical, Medical, and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
⁵ Dermatology Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy
⁶ Dermatology Department, Cheikh Khalifa International University Hospital, Mohammed VI University of Health Sciences (UM6SS), Casablanca, Morocco
⁷ Dermatology Division of the Instituto de Investigaciones Médicas Alfredo Lanari, University of Buenos Aires (UBA), Argentina
⁸ Dermatology Department, UHC Hassan II, Fez, Morocco
⁹ Dermatologie Maldegem – Maldegem, Belgium
¹⁰ Department of Dermatology, Hospital del Mar-Parc de Salut Mar, Barcelona, Spain
¹¹ Department of Dermatology and Venerology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
¹² Region Västra Götaland, Sahlgrenska University Hospital, Department of Dermatology and Venerology, Gothenburg, Sweden
¹³ Department of Clinical Medicine and Surgery, Section of Dermatology, University of Naples Federico II
¹⁴ Department of Dermatology, Venerology and Allergology, Faculty of Medicine, Medical University of Gdańsk, Poland
¹⁵ Dermatologic Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

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Corresponding author: Gloria Orlando, Dermatology Unit, Department of Medicine - DIMED, University of Padova, Italy.
E-mail: gloriaorlando@gmail.com
Frontal fibrosing alopecia (FFA), first described by Kossard in 1994 [1,2], is a form of primary lymphocytic scarring alopecia characterized by a progressive hand-like recession of the fronto-temporal hairline and, in 50-75% of cases, by a partial or complete alopecia of the eyebrows. Whether FFA is only a form of lichen planopilaris (LPP) or a more complex disorder is still a matter of debate [3-5].

Thousands of cases have been described to date, with increasing incidence of the disease worldwide. Postmenopausal women are still those primarily affected, but women with childbearing potential and males can also present with this disease [6-8]. Scalp FFA can also present in atypical forms such as linear, diffuse, zig-zag, and pseudo-fringe patterns [9]. Hair follicles on the occipital scalp and sideburns can also be involved as well as eyelashes, beard, axillae, limbs and pubis [10-12]. Lichen planus pigmentosus, facial papules and facial erythema have also been described in patients with FFA indicating that this is not necessarily a disease limited to the scalp and eyebrows [13-15].

The real incidence of FFA is unknown, but the important increase in the reported cases in recent years has led some authors to refer to it as an epidemic disease [16]. The etiopathogenesis and the reason for the increasing incidence of FFA are still unknown. The fact that FFA develops later in life suggests that triggering environmental factors might play a role in the development of the disease. A genetic basis has also been hypothesized since FFA has been diagnosed in siblings and members of the same family [17, 18]. Although FFA is thought to be a variant of LPP, there is no reported association with HLA-DR1. A recent genome-wide association study showed that FFA correlates with the HLA-B*07:02 allele [19]. Lastly, it has been speculated that the disease was present even before Kossard’s first description, but somehow passed unnoticed [20].

Due to the lack of randomized clinical trials and lack of a control group in previous clinical studies, treatment of FFA is not evidence-based [21]. Lack of evidence doesn’t mean, however, lack of effectiveness. Disease control might be achieved with topical, intralesional and oral treatments, often combined together. The treatment aim is always to stop disease progression [22].

At present, although the clinical picture of FFA is very typical in most cases, a biopsy for histopathological confirmation is still recommended to administer the correct treatment [23]. In cases not involving the scalp, a biopsy is mandatory. Scarring might be subtle and the fibrous tracts so thin that the loss of follicular ostia might be missed. Thus, FFA can be mistaken for a nonscarring alopecia, particularly alopecia areata (AA) and androgenic alopecia (AGA). Moreover, due to the presence of the disease in cosmetically sensitive areas, patients do not always accept biopsy even if it is a 2-mm punch biopsy [24]. For these reasons, modern noninvasive techniques including dermoscopy [25-27], reflectance confocal microscopy [28] and optical coherence tomography [29] are increasingly used to diagnose several skin and mucosal inflammatory diseases. The goal is to perform a diagnosis without the necessity of a biopsy and to reserve it only for early stages, doubtful cases and/or uncommon presentations.

Therefore, the International Dermoscopy Society (IDS) aimed to test the ability of its members to diagnose typical or classic FFA through clinical and dermoscopic parameters and to compare the acquired data to the largest cohort studies published since 1994.
Methods

The study was launched by the IDS via an online call for contributions published on the IDS website (www.dermoscopy-ids.org). From March 2018 to March 2020, IDS members were invited to submit cases of FFA. High quality clinical and dermoscopic images of the clinical presentations were mandatory. Information on patient demographics and lesion characteristics were also required including age, gender, involved skin/scalp areas, time at onset, subjective symptoms and trichoscopic features. Furthermore, information regarding the diagnostic methodologies were also mandatory. The study was conducted in accordance with ethical guidelines, and IRB approval was obtained. All data were collected and analyzed.

A literature search for “frontal fibrosing alopecia” was then performed on PubMed and returned 502 items (April 2021). Only papers reporting more than 100 cases were considered and revised. For each paper the year of publication, the number of patients, the origin of the population, the type of diagnostic methodology was collected.

Results

After the initial call, 206 FFA cases from 10 different centres were collected, but 18 cases were excluded from analysis due to misdiagnosis (8.7%). The clinical and trichoscopic data of all 188 included cases are presented in Table 1. The mean age of the studied population was 62 years (range 40–84) with a predominant female population (98.4%) and only 3 male patients. The great majority of the female population were post-menopausal (88.1%) with an average age of climacteric onset at 44.3 years. The mean age at onset of the disease was 58.6 years, on average 11.2 years after menopause. However, the disease was diagnosed up to 35 years after menopause. Regarding the degree of disease at diagnosis, 51.6% of the patients already showed grade 2 disease at that timepoint. When the frontal scalp was involved, the mean recession of the hairline was 2.35 cm (0-10 cm) and the distance between the glabella and the forehead was 7.57 cm (range 5-15 cm). FFA also affected the parietal regions in 70.2% of cases (132/188), while the occipital region was involved in 11.7% of cases (22/188). The sideburns were not affected in any of the patients.

Reduction or complete loss of eyebrows was reported in 85.6% of patients with partial loss in 104 patients (55.3%) and total loss in 56 patients (29.8%). The beard was involved only in one male patient, whereas involvement of eyelashes, armpits and pubis were reported in 52 (27.6%), 80 (42.5%) and 68 (36.1%) patients, respectively. In all cases with an extra-scalp involvement, the eyebrows were also compromised at the same time. Non-inflammatory facial papules were observed in 56 patients (29.8%). In 48 patients, they

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>188 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Severity</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>37 (19.6%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>97 (51.6%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>45 (23.9%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>7 (3.7%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>2 (1%)</td>
</tr>
<tr>
<td><strong>Clinical Data</strong></td>
<td></td>
</tr>
<tr>
<td>Recession</td>
<td>2.35 (0-10) cm</td>
</tr>
<tr>
<td>Glabella-hairline distance</td>
<td>7.57 (5-15)</td>
</tr>
<tr>
<td>Occipital area involvement</td>
<td>11.7% (22/188)</td>
</tr>
<tr>
<td>Parietal area involvement</td>
<td>70.2% (132/188)</td>
</tr>
<tr>
<td>Eyebrows involvement</td>
<td>85.6% (161/188)</td>
</tr>
<tr>
<td>Eyelashes involvement</td>
<td>27.6% (52/188)</td>
</tr>
<tr>
<td>Body hairs involvement</td>
<td>47.3% (89/188)</td>
</tr>
<tr>
<td>Armpits hairs involvement</td>
<td>42.5% (80/188)</td>
</tr>
<tr>
<td>Pubis hairs involvement</td>
<td>36.1% (68/188)</td>
</tr>
<tr>
<td>Beard (<em>men only</em>)</td>
<td>33.3% (1/3)</td>
</tr>
<tr>
<td>Facial papules</td>
<td>29.8% (56/188)</td>
</tr>
<tr>
<td><strong>Scalp symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>65.9% (124/188)</td>
</tr>
<tr>
<td>Trichodynia</td>
<td>22.9% (43/188)</td>
</tr>
<tr>
<td><strong>Trichoscopy</strong></td>
<td></td>
</tr>
<tr>
<td>Empty follicles</td>
<td>93.6% (176/188)</td>
</tr>
<tr>
<td>Absence of follicular ostia</td>
<td>92% (173/188)</td>
</tr>
<tr>
<td>Perifollicular erythema</td>
<td>63.8% (129/188)</td>
</tr>
<tr>
<td>Follicular hyperkeratosis</td>
<td>60.1% (113/188)</td>
</tr>
<tr>
<td>Lonely hairs</td>
<td>54.8% (103/188)</td>
</tr>
<tr>
<td><strong>Clinical associations</strong></td>
<td></td>
</tr>
<tr>
<td>AGA</td>
<td>38.8% (73/188)</td>
</tr>
<tr>
<td>Lichen planopilaris</td>
<td>18.6% (35/188)</td>
</tr>
<tr>
<td>Lichen planus (skin/mucosae/nails)</td>
<td>5.3% (10/188)</td>
</tr>
<tr>
<td><strong>Diagnostic methods</strong></td>
<td></td>
</tr>
<tr>
<td>Dermoscopy</td>
<td>71.8% (135/188)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>28.2% (53/188)</td>
</tr>
</tbody>
</table>

FFA=frontal fibrosing alopecia; AGA= androgenetic alopecia
were localized on the face, in 6 patients on the limbs and in 2 patients simultaneously on the face, limbs and trunk.

Concomitant signs of LPP on the scalp were present in 35 patients (18.6%). Five of them showed diffuse hair thinning in the crown area associated with trichoscopic and histopathological features of LPP and were diagnosed with fibrosing alopecia in a pattern distribution (FAPD). Ten out of 188 patients (5.3%) had lichenoid changes on the skin, mucous membranes and/or nails. The concomitant presence of AGA was found in 73 patients (38.8%).

A family history of FFA was reported in 19 patients (10.1%) with a mean age of onset at 56.4 years, while it was 59.6 years in patients without a family history (P = 0.9).

Trichoscopy reports showed signs of cicatricial alopecia in all patients, with empty follicles in 93.6% of cases and absence of follicular ostia in 92% of cases. The presence of inflammatory signs such as perifollicular erythema and perifollicular hyperkeratosis were present in 129 (63.8%) and 113 (60.1%) of the patients, respectively. One hundred and three patients (54.8%) presented lonely hairs. Trichoscopic signs were not associated with the degree of disease, but clinical signs of inflammation such as perifollicular erythema and perifollicular hyperkeratosis were associated with the presence of pruritus (P = 0.049). Indeed, 124 patients (65.9%) complained of itching and 43 (22.9%) reported concomitant trichodynia.

In most cases (71.8%), the characteristic clinical presentation (Figure 1) and the typical trichoscopic findings (Figure 2) made it possible to make the diagnosis of FFA without resorting to the use of invasive diagnostic techniques. Only 53 patients required a histopathological diagnosis.

The literature search identified a total of 24 papers (all published between 2014 and 2021) with more than 100 included cases (Table 2) [19, 25-27, 30-49]. During 2014, 2015, and 2016 only one study was published per year [25,48,49]. Two and 5 studies were published in 2017 and

![Figure 1. Clinical presentation of a female with frontal fibrosing alopecia.](image1)

![Figure 2. Trichoscopy of a female affected by frontal fibrosing alopecia.](image2)

**Table 2. Data of Published Studies on FFA Reporting more than 100 Cases**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Sex M/F</th>
<th>Population</th>
<th>Type of diagnosis</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muller Ramos P et al 2021 [31]</td>
<td>451</td>
<td>18/433</td>
<td>Brazil</td>
<td>NA</td>
<td>Multicenter case-control study on risk factors for FFA</td>
</tr>
<tr>
<td>Grassi S et al 2021 [32]</td>
<td>119</td>
<td>8/111</td>
<td>Italy</td>
<td>NA</td>
<td>Retrospective observational monocentric study on epidemiology, clinical and trichoscopic features and comorbidities in FFA patients</td>
</tr>
<tr>
<td>Trager MH et al 2021 [33]</td>
<td>173</td>
<td>14/159</td>
<td>Colombia and USA</td>
<td>Clinical and histopathological</td>
<td>Retrospective cohort study on medical comorbidities and gender distribution among patients with LPP and FFA</td>
</tr>
<tr>
<td>McSweeney SM et al 2020 [34]</td>
<td>711</td>
<td>0/711</td>
<td>UK</td>
<td>Clinical (histopathological when needed)</td>
<td>Descriptive cross-sectional study on clinical phenotype in women from FFA UK GWAS cohort</td>
</tr>
</tbody>
</table>

Table 2 continues
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Number of patients</th>
<th>Sex M/F</th>
<th>Population</th>
<th>Type of diagnosis</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzai A et al 2019 [27]</td>
<td>151</td>
<td>0/151</td>
<td>Brazil/Italy</td>
<td>Histopathological</td>
<td>Retrospective and prospective study on trichoscopic findings of FFA of the eyebrows</td>
</tr>
<tr>
<td>Papanikou S et al 2019 [35]</td>
<td>100</td>
<td>0/100</td>
<td>Greece</td>
<td>NA</td>
<td>Observational study on the influence of social status on the prognosis of FFA in female patients</td>
</tr>
<tr>
<td>Mulinari Brenner F et al 2019 [36]</td>
<td>227</td>
<td>NA</td>
<td>Brazil</td>
<td>NA</td>
<td>Observational study on reported cases of FFA in a tertiary center</td>
</tr>
<tr>
<td>Vañó-Galván et al 2019 [37]</td>
<td>306</td>
<td>NA</td>
<td>Australia, Brazil, Chile, Colombia, Italy, Mexico, Norway, Poland, Portugal, South Africa, Spain, Switzerland, USA and UK</td>
<td>NA</td>
<td>Retrospective multicenter study on frequencies of alopecia types at 22 specialized hair clinics</td>
</tr>
<tr>
<td>Kanti V et al 2019 [38]</td>
<td>490</td>
<td>25/465</td>
<td>France and Germany</td>
<td>Clinical (histopathological when needed)</td>
<td>Observational cross-sectional descriptive study on demographic and clinical characteristics associated with the severity of FFA</td>
</tr>
<tr>
<td>Moreno-Arrones OM et al 2019 [39]</td>
<td>278</td>
<td>0/278</td>
<td>Spain</td>
<td>Clinical (histopathological when needed)</td>
<td>Multicenter cross-sectional study on factors influencing FFA severity</td>
</tr>
<tr>
<td>Tziotzios C et al 2019 [19]</td>
<td>1016</td>
<td>0/1016</td>
<td>Greece and UK</td>
<td>NA</td>
<td>Genome-wide association study on FFA</td>
</tr>
<tr>
<td>Moreno-Arrones OM et al 2019 [40]</td>
<td>335</td>
<td>20/315</td>
<td>Spain</td>
<td>NA</td>
<td>Multicenter case-control study on risk factors associated with FFA</td>
</tr>
<tr>
<td>Cranwell WC et al 2019 [41]</td>
<td>130</td>
<td>0/130</td>
<td>Australia</td>
<td>NA</td>
<td>Case-control questionnaire study on exposure to sunscreen or facial skin care products and their association with FFA</td>
</tr>
<tr>
<td>Buendia-Castano D et al 2018 [42]</td>
<td>104</td>
<td>0/104</td>
<td>Spain</td>
<td>Clinical (histopathological when needed)</td>
<td>Case-control study on hormonal and gynecological risk factors for FFA</td>
</tr>
<tr>
<td>Imhof RL et al 2018 [43]</td>
<td>148</td>
<td>0/148</td>
<td>USA</td>
<td>Clinical (histopathological when needed)</td>
<td>Retrospective study on clinicopathological findings, comorbidities and treatment outcomes in women with FFA</td>
</tr>
<tr>
<td>Saceda-Corralo D et al 2018 [44]</td>
<td>103</td>
<td>0/103</td>
<td>Spain</td>
<td>Clinical (histopathological when needed)</td>
<td>Descriptive cross-sectional study on patients diagnosed with both FFA and LPP</td>
</tr>
<tr>
<td>Cervantes J et al 2018 [26]</td>
<td>108</td>
<td>NA</td>
<td>USA</td>
<td>Clinical (histopathological when needed)</td>
<td>Retrospective study on trichoscopic features of sideburns in FFA compared to fronto-temporal scalp</td>
</tr>
<tr>
<td>Pindado Ortega C et al 2018 [45]</td>
<td>103</td>
<td>0/103</td>
<td>Spain</td>
<td>Clinical (histopathological when needed)</td>
<td>Descriptive cross-sectional study on relationship between FFA and rosacea</td>
</tr>
<tr>
<td>Donati A et al 2017 [46]</td>
<td>149</td>
<td>NA</td>
<td>France</td>
<td>Clinical (histopathological when needed)</td>
<td>Retrospective analysis on the use of direct immunofluorescence in FFA</td>
</tr>
</tbody>
</table>

*Table 2 continues*
Table 2. Data of Published Studies on FFA Reporting more than 100 Cases (continued).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Sex M/F</th>
<th>Population</th>
<th>Type of diagnosis</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreno Arrones OM et al 2017 [47]</td>
<td>242</td>
<td>0/242</td>
<td>Spain</td>
<td>Clinical (histopathological when needed)</td>
</tr>
<tr>
<td>Aldoori N et al 2016 [48]</td>
<td>105</td>
<td>0/105</td>
<td>UK</td>
<td>Clinical</td>
</tr>
<tr>
<td>Vañó-Galván et al 2014 [49]</td>
<td>355</td>
<td>12/343</td>
<td>Spain</td>
<td>Clinical (histopathological when needed)</td>
</tr>
</tbody>
</table>

FFA = frontal fibrosing alopecia; F = females; M = males; NA = not applicable.

2018, respectively [26,42-47]. Nine studies were released in 2019 [19,27,35-41] and 5 studies were published in 2020 and 2021 [30-34]. In 13 studies, clinical and trichoscopic features were decisive for the diagnosis in almost all FFA cases [26,30,34,39,42-49]. Invasive biopsies for histopathological examinations were reserved for doubtful cases and confirmed the diagnosis in all cases.

Conclusions

Since its first description in 1994, FFA has shown a significant increase in incidence all over the world. In 2014, Vañó-Galván et al published the first large cohort of patients diagnosed with FFA [49]. Subsequently, as confirmed by our review of the literature, the number of published large cohort studies have increased over time, in particular during the last 3 years. Of note, Tziotzios et al published the largest cohort study in 2019, reporting more than 1,000 patients from Greece and UK [19]. Here, we report an additional large cohort of patients diagnosed with FFA collected through IDS members who responded to our online call.

The mean age at onset of the disease in our sample was 58.6 years, which is comparable to the previously reported data on FFA. The results support the current theory that the disease mainly affects postmenopausal women (88.1%), but also documents that it can be found in younger women (11.9%). The youngest patient was 15 years old at the onset of symptoms. Our sample also included 3 male subjects supporting the fact that FFA can affect males as well. Cases of FFA within multiple members of the same family have been reported in 5-8% of the cases [49, 50], a result that is a very similar to the percentage observed in our study (10.1%).

Navarro Belmonte et al reported that the age at onset of the disease in cases with relatives affected by FFA appears to be lower than in isolated cases [51]. Our study also showed an earlier onset of about 3 years in subjects with a positive family history. However, the difference between the two groups was not significant in our cases.

In accordance with other small studies [8,52], our study reported an association between FFA and LPP (18.6% of cases) including 5 patients with FAPD. This observation supports the theory that FFA could actually represent a clinical variant of LPP despite the different symptoms. Although this association was not reported in larger studies, it is possible that it is under-reported.

Consistent with previous studies [53,54], the presence of AGA was recorded in 38.8% of patients suggesting that AGA may be at the root of a fibrotic process leading to FFA or that FFA and AGA may have a similar underlying pathogenetic mechanism, for example a hormonal basis. The role of hormones is however still uncertain and debated as well as the link between FFA, LPP and AGA. One retrospective study associated FFA with androgen deficiency, while LPP was more frequently associated with androgen excess [54]. Furthermore, no association with Lupus and AA was reported in our group of patients.

Interestingly, the diagnosis of FFA in our cohort was made on average 4.4 years after the onset of the disease and in 51.6% of cases already presented as grade 2 of severity with a mean frontal hairline recession of 2.35 cm, which in some cases reached 10 cm. This underlines the importance of awareness and education on this disease, not only among patients but also among health professionals, in order to diagnose and treat FFA at an earlier stage to stop the scarring process.
Alopecia of the eyebrows, found in 85.6% of cases, was confirmed as the most frequent sign of the disease, while the loss of eyelashes and axillary, pubic and/or body hair was documented with a lower rate. Some authors have raised the doubt that the peripheral involvement of the disease could actually be simply a consequence of menopause and/or aging [55]. In this regard, we compared patients of childbearing age with menopausal patients and found overlapping percentages of body hair involvement in both age groups (86.4% versus 87.1%). Therefore, these observations seem to confirm the frequent involvement of various anatomical regions of FFA. In particular, eyebrow involvement could play a significant role in early diagnosis since, in many cases, thinning or loss of the eyebrows precedes the recession of the fronto-temporal hairline. Eyebrows and body hair reduction/loss are often confused with age-related loss and seldom reported by patients themselves. Thus, awareness of this sign possibly indicating FFA is important when considering differential diagnoses such as AA or aging [56]. Moreover, the finding of non-inflammatory facial papules was described in 29.8% of patients, suggesting that this sign should always be sought in cases of suspected FFA.

Even if the clinical diagnosis is most often easy to perform, trichoscopy is a valid aid in milder cases and in evaluation of facial/body hair loss. Trichoscopy is also a valid aid in the differential diagnosis with other diseases such as AGA, traction alopecia or AA in which there is no scarring. Interestingly, trichoscopic cicatricial signs were absent in a small percentage of patients, suggesting that FFA could likely begins as a non-scarring process. Consequently, early treatment could partially recover damaged follicles.

The presence of inflammatory signs such as perifollicular erythema and perifollicular hyperkeratosis were present in 63.8% and 60.1% of patients, respectively, and were associated with the presence of dysaesthetic sensations such as trichodynia and pruritus (P = 0.049). Previous studies report that up to one-third of patients with FFA may have itching and, less frequently, trichodynia. However, our series revealed higher percentages of symptomatic subjects with 65.9% of patients complaining of itching and 22.9% reporting concomitant trichodynia.

In most cases (71.8%) the characteristic clinical presentation and the typical trichoscopic findings allowed the diagnosis of FFA. The relevant role of the clinical and trichoscopic features in performing the diagnosis was also confirmed by the literature review. Indeed, in most studies they were decisive for the diagnosis confirming that trichoscopy is a worldwide-acknowledged non-invasive technique for the diagnosis of FFA. Further studies are necessary to evaluate the role of other in vivo non-invasive imaging techniques such as reflectance confocal microscopy, optical coherence tomography, diffuse reflection spectrophotometry and ultrasound in the investigation of FFA to reduce the need of surgical biopsies and histopathological confirmation of the disease.

References


Study of Nail Psoriasis and Dermoscopic Correlation with Dermoscopic and Modified Dermoscopic Nail Psoriasis Severity Indexes (dNAPSI and dmNAPSI)

Sandeep Arora¹, Debatraya Paul², Richa Kumar³, Anuj Bhatnagar², Gulhima Arora⁴, Sunita Mech², Devinder Kumar Suhag²

1 Department of Dermatology, Army College of Medical Sciences & Base Hospital Delhi Cantt, India
2 Command Hospital Air Force Bangalore, India
3 Command Hospital Eastern Command Kolkota, India
4 Mehektagul Dermaclinic, New Delhi, India

Key words: Nail psoriasis, nail psoriasis severity index, psoriasis area severity index, dermoscopy, onychoscopy

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Corresponding author: Sandeep Arora, Army College of Medical Sciences & Base Hospital Delhi Cantt, India. E-mail: aroraderma@gmail.com

ABSTRACT

Background: Nail involvement in psoriasis may be assessed clinically, ultrasonologically, and dermoscopically. The aim of this study was to assess the dermoscopic features of nails in psoriasis, to compare them with the clinical findings, and to correlate them with the Nail Psoriasis Severity Index (NAPSI) score.

Methods: We recruited 120 patients with psoriatic nail changes for the study. The Psoriasis Area Severity Index (PASI) was used to assess the severity of disease. Clinical and dermoscopic (DermLite DL4, ×10, polarized and non-polarized) nail examination determined NAPSI, modified NAPSI (mNAPSI), and NAPSI determined with dermoscopic findings (dermoscopic NAPSI [dNAPSI] and dermoscopic modified NAPSI [dmNAPSI]) were used to assess severity of nail involvement.

Results: Subungual hyperkeratosis (50.8%) and nail plate thickening (56.7%) were the commonest clinical nail changes found, and dermoscopically, they were subungual hyperkeratosis and pitting (68.3% each). The average median with interquartile range of PASI and NAPSI scores were 7.5 [5.7-10.8] and 8.0 [6-12], respectively. NAPSI increased significantly with increased in PASI scores (P < 0.001). A comparison of NAPSI and mNAPSI with dNAPSI and dmNAPSI revealed that NAPSI, mNAPSI, and dNAPSI increased significantly with an increase in PASI scores. The dNAPSI scores increased significantly with increased mNAPSI and dmNAPSI, and mNAPSI and dmNAPSI were significantly good predictors of joint involvement in psoriasis.

Conclusions: Dermoscopy allows for better visualization of nail findings. Evaluating NAPSI and mNAPSI scores in conjunction with dNAPSI and dmNAPSI increases their helps detect early psoriasis, detection of worsening moderate-to-severe psoriasis (PASI >10) and predict joint involvement and their severity.
Introduction

Nail changes in psoriasis are significant findings and associated with a significant psychological impact [1]. Nail lesions are observed in about one-half of patients with psoriasis, with an estimated lifetime incidence of 80-90% [2]. Most psoriasis cases present with nail changes, while isolated nail psoriasis is rare, occurring in 1-5% of patients [3]. These changes are most common in older patients, in severe forms of psoriasis, in cases with longer duration of disease, and in the presence of psoriatic arthritis, in which case the incidence of nails changes is over 80% [4]. More severe nail psoriasis is associated with a more severe cases of psoriatic arthritis [5].

The clinical presentation of nail psoriasis varies according to the severity and localization of the lesion: the nail matrix, the nail bed, and in severe forms, the entire nail structure [6,7]. The most common nail lesion reported is pitting, followed by nail bed discoloration, onycholysis, subungual hyperkeratosis, abnormalities of the nail plate, and splinter hemorrhages [8]. They lead to significant functional impairment, pain, and psychosocial distress, and patients report significantly worse values in satisfaction with their treatment due to the stress and time involved in treatment [2,9].

Dermoscopy with polarized and non-polarized modes is useful in the evaluation of superficial nail plate/matrix changes, such as pitting and crumbling, and deeper nail bed psoriatic nail involvement in the form of onycholysis, oil spots, subungual hyperkeratosis and splinter hemorrhages, especially when there are no typical clinical features [10,11].

Objectives

The focus of our study was to determine the frequency of dermoscopic findings in psoriatic nails and to compare the dermoscopic examination with the clinical examination to investigate the relationships between the indicators of disease severity.

Methods

This was a prospective observational study conducted from October 2018 to October 2019 in the Department of Dermatology in a tertiary care teaching hospital. Approval from the institutional ethics committee of Command Hospital Air Force Bangalore was obtained vide EC/CHAF Bangalore/2018/27 dated 14 May 2018. Clinically diagnosed psoriasis patients who visited the dermatology Outpatient Clinic were screened, and 120 patients aged 14-75 years with nail psoriasis were examined clinically and with dermoscope (DermLite DL4, ×10; polarized and non-polarized modes). Onychomycosis was ruled out after performing KOH mount on nails and fungal cultures from all the suspected cases. Patients with coexisting onychomycosis, erythrodermic psoriasis, patients in remission following systemic treatment for psoriasis, pregnant women, patients not consenting to the study, and patients with systemic disorders that may have influenced nail changes were excluded from the study. The clinical-demographic profile of the participants was documented. Clinical images of the hands and feet and radiographs were taken, and the Classification Criteria for Psoriatic Arthritis (CASPAR) scores were calculated.

Disease severity was assessed using Psoriasis Area Severity Index (PASI) as a clinical assessment tool for each patient. All nails were examined clinically followed by a dermoscopic examination. Dermoscopic images were captured with DermLite DL4, ×10, polarized and non-polarized modes. The Nail Psoriasis Severity Index (NAPSI) and modified NAPSI (mNAPSI) scores were calculated for both fingernails and toenails. With dermoscopic findings we recalculated NAPSI and labeled it dermoscopic NAPSI (dNAPSI) and dermoscopic modified NAPSI (dmNAPSI).

Statistical Analysis

All characteristics were summarized. For continuous variables, the summary statistics of mean ± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. If the P-value/ Z-value was < 0.05, then the results were statistically significant; otherwise, they were considered as not statistically significant. A receiver operating characteristic (ROC) curve was plotted for NAPSI, dNAPSI, dmNAPSI, and mNAPSI to compare their predictive ability for clinical joint involvement. The odds ratio of NAPSI and dmNAPSI to their correlation with CASPAR was also analyzed. Data were analyzed using SPSS software v.23.0.

Results

A total of 120 patients with psoriatic nail involvement were included in the study. The mean age of the patients was 47.3 ± 13.1 years (range 14-74 years). Fifty-five percent of patients had the disease for more than 5 years, and the duration of treatment ranged from 0.2 to 11 years (4.9 ± 2.6 years). The mean body mass index (BMI) of the study population was 26.3 ± 3.2 kg/m². Hypertension was the commonest comorbidity (Table 1).

Chronic plaque psoriasis was the commonest clinical presentation (79.2%) and 72.5% of the patients had a PASI score <10; 51.7% of study subjects had a NAPSI score between 6 and 10. Arthritis was noted in 11.7% of cases (n = 14), 90% (n = 108) had a CASPAR score of 3 or more. The mean numbers of fingernails and toenails affected were 3.5 ± 1.2 and 3.6 ± 1.5 with a mean NAPSI score of 10.1 ± 6.1. A larger number of nail changes were detected with dermoscopy. Nail

2
Table 1. Socio-Demographic Details of Patients (n=120)

<table>
<thead>
<tr>
<th>Demographic Details</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age-group, years</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>16 (13.3)</td>
</tr>
<tr>
<td>31-40</td>
<td>18 (15.0)</td>
</tr>
<tr>
<td>41-50</td>
<td>33 (27.5)</td>
</tr>
<tr>
<td>51-60</td>
<td>35 (29.2)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>18 (15.0)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>99 (82.5)</td>
</tr>
<tr>
<td>Females</td>
<td>21 (17.5)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) (Asia-Pacific guidelines)[17]</strong></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>01 (0.8)</td>
</tr>
<tr>
<td>Normal (18.5 - 22.9)</td>
<td>16 (13.3)</td>
</tr>
<tr>
<td>Overweight (23.0 - 24.9)</td>
<td>28 (23.3)</td>
</tr>
<tr>
<td>Obese Class I (25.0 - 29.9)</td>
<td>56 (46.7)</td>
</tr>
<tr>
<td>Obese Class II (≥ 30.0)</td>
<td>19 (15.8)</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 6 months</td>
<td>07 (05.8)</td>
</tr>
<tr>
<td>6 – 12 months</td>
<td>12 (10.0)</td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>35 (29.2)</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>66 (53.0)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (24.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (15.8)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>14 (11.7)</td>
</tr>
<tr>
<td>Others</td>
<td>02 (01.7)</td>
</tr>
</tbody>
</table>

BMI = body mass index.

Matrix signs were noted in 95.8 % of cases and nail bed signs were noted in 85.0% of cases. Clinically, nail plate thickening (56.7%) and subungual hyperkeratosis (50.8%) were the most common presentations and, on dermoscopic examination, pitting (72.5%) and subungual hyperkeratosis (68.3%) the most frequent ones (Figure 1) (Table 2).

The mean (range) of PASI, NAPSI, mNAPSI, dNAPSI and dmNAPSI scores were 7.5 (1.8-36.0), 8.5 (3-39), 7.0 (0-34), 11.0 (3-45) and 11.0 (0-44), respectively. NAPSI, mNAPSI and dNAPSI scores increased significantly with the rise in PASI scores (r = 0.56, P < 0.001), (r = 0.57, P < 0.001) and (r = 0.54, P < 0.001), respectively (Figures 2 and 3).

The scores of dNAPSI also increased significantly with the increase of mNAPSI and dmNAPSI scores (r = 0.84 with P < 0.001 and r = 0.87 with P < 0.001, respectively) (Figure 4).

Keeping the variables like age, gender, BMI, NAPSI scores, presence of comorbidities, duration of onset of disease, and duration of treatment constant in for analysis the increase in dNAPSI scores by 1 unit is likely to detect PASI scores <10 by 1.08 times and PASI scores between 10 and 20 by 0.69 times compared to PASI scores >20. Similarly, the increase in dmNAPSI scores by 1 unit is less likely to detect PASI scores <10 by 0.59 times and PASI scores between 10 and 20 by 0.69 times compared to PASI scores >20.

The adjusted odds values showed that dNAPSI scores were more likely to detect psoriasis at an early stage compared to NAPSI and dmNAPSI. Although the scores were not significant predictors in detecting psoriasis at an early stage (P > 0.05) (Table 3), dNAPSI was likely to detect a rise in PASI in moderate-to-severe psoriasis better than NAPSI. Hence, follow-up of cases with this index can alert an impending worsening of the condition.

The receiver operating characteristic (ROC) curve plotted for NAPSI, dNAPSI, dmNAPSI, and mNAPSI to compare their predictive ability for clinical joint involvement revealed that mNAPSI and dmNAPSI were significantly better predictors of joint involvement compared to other nail psoriasis severity indices (NAPSI, dNAPSI) (P < 0.05) (Figure 5).

There were no cases with PASI scores <10 in the current study, therefore the sensitivity of NAPSI, dNAPSI, mNAPSI, and dmNAPSI was not evaluated. The scores of NAPSI, dNAPSI, dmNAPSI, and mNAPSI were statistically significant (P > 0.05) for joint involvement, and their sensitivity to detect psoriasis of severity was as follows: NAPSI (88.9%), dNAPSI (91.7%), dmNAPSI (93.3%), and mNAPSI (95.8%). The ROC curves for NAPSI, dNAPSI, dmNAPSI, and mNAPSI to compare their predictive ability for clinical joint involvement revealed that mNAPSI and dmNAPSI were significantly better predictors of joint involvement compared to other nail psoriasis severity indices (NAPSI, dNAPSI) (P < 0.05) (Figure 5).

The mean ranks of mNAPSI increased significantly with the duration of the disease (1-6 months = 47.57; 12-60 months = 60.00; >60 months = 67.34, with P < 0.05), except at 6-12 months (31.88, P > 0.05). The mean ranks of other scores, ie dNAPSI, dmNAPSI and NAPSI, did not vary significantly in relation to the durations of the disease (P > 0.05) (Table 4).

The mean ranks of mNAPSI increased significantly with the duration of the disease (1-6 months = 47.57; 12-60 months = 60.00; >60 months = 67.34, with P < 0.05), except at 6-12 months (31.88, P > 0.05). The mean ranks of other scores, ie dNAPSI, dmNAPSI and NAPSI, did not vary significantly in relation to the durations of the disease (P > 0.05) (Table 5).

Conclusions

Dermoscopy allows for better visualization of the nail bed and nail matrix abnormalities, and detects early or mild, as well as late changes in the disease, as was also seen in the present study [12]. With its routine use in clinical practice, early and late descriptions of skin, nail and hair diseases are being elaborated in literature increasingly. However, their relevance and importance to standard clinical findings need...
Table 2. Frequency Distribution of Clinical and Dermoscopic Nail Bed and Nail Matrix Findings Among Patients

<table>
<thead>
<tr>
<th>Findings</th>
<th>Clinical Examination</th>
<th>Dermoscopic Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (n)</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td><strong>Nail Bed Signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>06</td>
<td>05.0</td>
</tr>
<tr>
<td>Subungual hyperkeratosis</td>
<td>61</td>
<td>50.8</td>
</tr>
<tr>
<td>Distal onycholysis</td>
<td>54</td>
<td>45.0</td>
</tr>
<tr>
<td>Oil drop sign</td>
<td>37</td>
<td>30.8</td>
</tr>
<tr>
<td>Dilated hyponychial capillaries</td>
<td>18</td>
<td>15.0</td>
</tr>
<tr>
<td><strong>Nail Matrix Signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail plate thickening</td>
<td>68</td>
<td>56.7</td>
</tr>
<tr>
<td>Pitting</td>
<td>60</td>
<td>50.0</td>
</tr>
<tr>
<td>Leukonychia</td>
<td>13</td>
<td>10.8</td>
</tr>
<tr>
<td>Transverse grooves</td>
<td>14</td>
<td>11.7</td>
</tr>
<tr>
<td>Trachyonychia</td>
<td>01</td>
<td>0.8</td>
</tr>
<tr>
<td>Red spots on lunula</td>
<td>04</td>
<td>03.3</td>
</tr>
<tr>
<td>Crumbling</td>
<td>23</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Figure 1. Dermoscopic image. (A) subungual hyperkeratosis. (B) pitting. (C) distal onycholysis. (D) splinter hemorrhages (DermLite DL4, ×10, polarized).
Figure 2. (A) Correlation of PASI and NAPSI scores. (B) Correlation of PASI and mNAPSI scores. mNAPSI = modified Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index.

Figure 3. Correlation of PASI and dNAPSI (dermoscopically assessed NAPSI) scores. dNAPSI = dermoscopic Nail Psoriasis Severity Index; PASI = Psoriasis Area Severity Index.

Chronic plaque psoriasis is known to be the commonest pattern of psoriasis, as evidenced in our study. The mean age of our cohort (47.3 ± 13.1 years) with psoriasis was similar to those reported literature [13]. In our study, we had 55% males and a duration of disease of 4.9 years, which is higher than other studies reporting nail findings [14,15]. Elobeid et al found a mean BMI of 25.3 kg/m², similar to our findings if not for a marginally higher BMI (26.3 kg/m²) which may have been due to different study populations and study settings [16][17].

In psoriasis, nail lesions usually manifest 10 years later than skin lesions, and nail involvement is present in 20%-50% of psoriatic patients [18-21]. According to Polat and Kapicioglu, the most common clinical and dermoscopic findings were pitting and leukonychia [12], and Wanniang et al noted salmon patch (oil drop sign) and splinter hemorrhages significantly better with the dermoscope [22]. In addition to pitting, Yorulmaz and Artuz found salmon patch (oil drop sign) to be associated with higher NAPSI scores [13]. However, in our study, pitting, subungual hyperkeratosis, nail plate thickening, and distal onycholysis were present in the majority of patients, and all nail changes were noted significantly better on dermoscopy. The difference in our observations from the reported literature may be due to different disease duration and severity with an average NAPSI score of 8 in our study versus 23, indicating higher disease severity among their patients [22]. Dermoscopic nail findings of subungual hyperkeratosis and oil drop signs were significantly associated with a higher median NAPSI score >8 in our study. The scores of NAPSI, mNAPSI and dNAPSI increased significantly with the rise in PASI scores, which partially corroborates the findings of studies by Hallaji et al and Prevezas et al [23,24].

The dNAPSI helped detect early psoriasis but did not perform well in detecting changes in severity in early psoriasis. However, dNAPSI was better than PASI at detecting worsening PASI in moderate-to-severe psoriasis.

Cassell et al formulated mNAPSI as a gold standard with good correlation with other disease severity measures [25]. The scores of dmNAPSI along with mNAPSI were found to be significantly better predictors of joint involvement compared to other nail psoriasis severity indices.

Both mNAPSI and dmNAPSI increased with severe joint involvement, based on the CASPAR criteria, with no statistically significant difference between these two scores. Hence, dmNAPSI is consistent as mNAPSI in correlation with joint severity.
Figure 4. (A) Correlation between dmNAPSI and dNAPSI scores. (B) Correlation between mNAPSI and dNAPSI scores. dNAPSI = dermoscopic Nail Psoriasis Severity Index; dmNAPSI = dermoscopic modified Nail Psoriasis Severity Index; mNAPSI = modified Nail Psoriasis Severity Index.

Table 3. Predictors of Severity of Nail Psoriasis Based on PASI Scores

<table>
<thead>
<tr>
<th>PASI Severity Scores</th>
<th>Measures of Nail Psoriasis Severity Index</th>
<th>Unadjusted Odds Ratio (OR)</th>
<th>Adjusted Odds Ratio (OR)</th>
<th>95% Confidence Interval (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>dNAPSI§</td>
<td>0.08</td>
<td>1.08</td>
<td>0.31 – 3.79</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>NAPSI</td>
<td>-0.36</td>
<td>0.69</td>
<td>0.25 – 1.99</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>dmNAPSI¥</td>
<td>-0.52</td>
<td>0.59</td>
<td>0.34 – 1.06</td>
<td>0.08</td>
</tr>
<tr>
<td>10-20</td>
<td>dNAPSI§</td>
<td>0.02</td>
<td>1.01</td>
<td>0.29 – 3.52</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>NAPSI</td>
<td>-0.36</td>
<td>0.69</td>
<td>0.25 – 1.95</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>dmNAPSI¥</td>
<td>-0.38</td>
<td>0.69</td>
<td>0.39 – 1.20</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Reference Category: PASI score more than 20; §-dermoscopic NAPSI; ¥-dermoscopic modified NAPSI
dNAPSI = dermoscopic NAPSI; dmNAPSI = dermoscopic modified NAPSI; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index

Figure 5. Predictive ability of NAPSI, mNAPSI, dmNAPSI, and dNAPSI in detecting joint involvement. dNAPSI = dermoscopic Nail Psoriasis Severity Index; dmNAPSI = dermoscopic modified Nail Psoriasis Severity Index; mNAPSI = modified Nail Psoriasis Severity Index; NAPSI = Nail Psoriasis Severity Index.
Table 4. Comparison of Measures of Nail Psoriasis Severity Indices as Predictors of Psoriatic Arthritis Based on CASPAR Criteria

<table>
<thead>
<tr>
<th>CASPAR Criteria</th>
<th>Measures of Nail Psoriasis Severity Index</th>
<th>Unadjusted Odds Ratio (OR)</th>
<th>Adjusted Odds Ratio (OR)</th>
<th>95% Confidence Interval (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>dNAPSI§</td>
<td>-0.02</td>
<td>0.99</td>
<td>0.48 - 2.02</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>mNAPSI</td>
<td>-0.79</td>
<td>0.46</td>
<td>0.15 - 1.35</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>NAPSI</td>
<td>0.46</td>
<td>1.58</td>
<td>0.54 - 4.62</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>dmNAPSI¥</td>
<td>0.74</td>
<td>2.10</td>
<td>0.69 - 6.45</td>
<td>0.19</td>
</tr>
<tr>
<td>3</td>
<td>dNAPSI§</td>
<td>-0.25</td>
<td>0.78</td>
<td>0.39 - 1.55</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>mNAPSI</td>
<td>-0.87</td>
<td>0.42</td>
<td>0.15 - 1.22</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>NAPSI</td>
<td>0.62</td>
<td>1.85</td>
<td>0.85 - 5.28</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>dmNAPSI¥</td>
<td>0.79</td>
<td>2.19</td>
<td>0.73 - 6.61</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>dNAPSI§</td>
<td>-0.31</td>
<td>0.74</td>
<td>0.35 - 1.54</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>mNAPSI</td>
<td>-0.75</td>
<td>0.48</td>
<td>0.16 - 1.40</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>NAPSI</td>
<td>0.71</td>
<td>2.03</td>
<td>0.68 - 6.02</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>dmNAPSI¥</td>
<td>0.76</td>
<td>2.13</td>
<td>0.69 - 6.52</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Reference Category: CASPAR criteria of 5; §-dermoscopic NAPSI; ¥ - dermoscopic modified NAPSI
CASPAR = Classification Criteria for Psoriatic Arthritis; dNAPSI = dermoscopic NAPSI; dmNAPSI = dermoscopic modified NAPSI; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index.

Table 5. Comparison of Mean Ranks of Nail Psoriasis Severity Index Among Different Durations of Onset of Disease in Months

<table>
<thead>
<tr>
<th>Measures of nail psoriasis severity index</th>
<th>Duration of Onset in Months</th>
<th>Z value (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-6 (n=7)</td>
<td>6-12 (n=12)</td>
</tr>
<tr>
<td>Mean ranks of dNAPSI§</td>
<td>53.07</td>
<td>69.38</td>
</tr>
<tr>
<td>Mean ranks of mNAPSI¥</td>
<td>47.57</td>
<td>31.88</td>
</tr>
<tr>
<td>Mean ranks of NAPSI</td>
<td>59.86</td>
<td>63.13</td>
</tr>
<tr>
<td>Mean ranks of dmNAPSI</td>
<td>43.79</td>
<td>45.12</td>
</tr>
</tbody>
</table>

¥-modified NAPSI; §-dermoscopic NAPSI; *statistically significant difference at P < 0.05
dNAPSI = dermoscopic NAPSI; dmNAPSI = dermoscopic modified NAPSI; NAPSI = Nail Psoriasis Severity Index.

The mean ranks of mNAPSI increased significantly with duration of onset of disease, except at 6-12 months. The mean ranks of other scores, ie dNAPSI, dmNAPSI and NAPSI, did not vary significantly across the durations of onset of disease.

Our aim in this study was to utilize the dermoscope to detect nail changes in psoriasis, and it revealed that nail changes are better visualized and detected earlier. Nail scoring for psoriasis utilizing dNAPSI helps in the early diagnosis and assessment and detection of worsening moderate-to-severe psoriasis (PASI >10) as compared to NAPSI. The use of dermoscopy for detecting joint severity as per CASPAR criteria was consistent with naked-eye assessment of nail findings. However, as none of these indices proved to be statistically significant by themselves, their true significance may be revealed with larger studies using dNAPSI and dmNAPSI. We do recommend the use of a dermoscope as a routine tool in assessing nail psoriasis.
References


24. Prevezas C, Katoulis AC, Papadavid E, Fanagakis P, Rigopoulos D. Short-Term Correlation of the Psoriasis Area Severity Index, the Nail Psoriasis Area Severity Index, and the Dermatology Life Quality Index, before and after Treatment, in Patients with Skin and Nail Psoriasis. Skin Appendage Disord. 2019;5(6):344-349. DOI: 10.1159/000499348.. PMID: 31799260; PMCID: PMC6883452.

Prevalence of Atherosclerosis in Psoriatic Patients Detected with Epiaortic Color Doppler Ultrasound and Computed Tomography Angiography

Annunziata Dattola¹, Guglielmo Manenti², Donatella Ferrari², Laura Vollono¹, Salvatore Marsico², Feliciana Lamacchia², Maria Esposito¹, Mattia Marchesano¹, Arianna Zangrilli¹, Roberto Floris², Alessandro Giunta¹, Luca Bianchi¹

¹Dermatology Department, University of Rome “Tor Vergata”, Rome, Italy
²Biomedicine and Prevention Department, UOC of Diagnostic Imaging, University of Rome “Tor Vergata”, Rome, Italy

Key words: psoriasis, color-doppler ultrasound, angio-CT, IMT, risk-factor


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Authorship: AD and GM have equally contributed to this article.

Corresponding author: Annunziata Dattola, MD, PhD. Dermatology Department, University of Rome “Tor Vergata”, Rome, Italy. E-mail: nancydattola@gmail.com

ABSTRACT

Introduction: Psoriasis (PsO), a chronic inflammatory, multisystemic, and multifactorial disease can cause endothelial dysfunction, artery calcification, and atherosclerotic disease. A higher incidence of vascular occlusive events has been observed in psoriatic patients compared to healthy controls, and multiple studies confirm the association between moderate-severe PsO and atherosclerosis, coronary artery calcification, and higher cardiovascular risk.

Objective: We sought to analyze atherosclerotic disease prevalence in epiaortic vessels of psoriatic and non-psoriatic patients to understand if PsO could represent an independent risk factor predisposing to atherosclerotic disease.

Methods: We evaluated 47 psoriatic patients without cardiovascular risk factors with color Doppler ultrasound (CDUS). If atheromatous plaques were detected, a computed tomography angiography (CTA) was performed. We evaluated 47 non-psoriatic patients without cardiovascular risk factors with CDUS. Atherosclerosis prevalence in both groups were statistically analyzed. CDUS performance was compared to CTA.

Results: In the psoriatic group (mean age 50.9 years), 6 had atheromatous plaques and 12 had an intima-media thickness (IMT) > 1 mm (overall prevalence of atherosclerotic disease: 38.2%). All plaques detected with CDUS were confirmed at CTA. In the control group (mean age 51.3 years),
Introduction

Psoriasis (PsO) is a chronic inflammatory, multisystemic, and multifactorial disease that affects about 3% of the world population [1]. The chronic systemic inflammatory process, that primarily affects the skin, also causes endothelial dysfunction, artery calcification, and atherosclerotic disease [2]. A higher incidence of vascular occlusive events has been observed in psoriatic patients compared to healthy controls, and multiple studies confirm the association between moderate-severe PsO and atherosclerosis, coronary artery calcification, and higher cardiovascular risk [3-8]. Young adults affected by severe PsO are 3 times more likely to face myocardial infarction than controls [9], and the risk of fatal myocardial infarction or stroke is even higher in patients hospitalized with PsO [10]. Moreover, a higher frequency of ischemic heart disease and cerebral and peripheral vascular disease has been observed in patients affected by moderate-severe disease compared with controls [11]. Thus, current opinion holds that PsO is an independent risk factor for cardiovascular disease [2,12,13].

Objectives

The aim of this study is to evaluate the prevalence of atherosclerotic disease in epiaortic vessels of psoriatic patients without conventional cardiovascular risk factors, using CDUS and CTA, and to analyze the presence of any difference in prevalence with non-psoriatic patients, in order to understand if PsO could be considered as an independent risk factor for atherosclerotic disease.

Methods

This study was conducted in collaboration between the Departments of Dermatology and Diagnostic Imaging at the University of Rome Tor Vergata. The study was conducted from January 2017 to July 2017 at the Department of Dermatology. We enrolled 280 consecutive patients (males and females) with psoriasis vulgaris or arthropathic psoriasis. The patients underwent clinical and laboratory exams, including abdominal circumference measurements and arterial pressure. We determined if the patients were cigarette smokers and if had hypercholesterolemia, hypertriglyceridemia, and glycemia.

The inclusion criteria of the study were: male and female patients aged 35-85 years, with an abdominal circumference < 102 cm for males and < 88 cm for females, cholesterol plasma level < 200 mg/dl, plasma glucose level < 126 mg/dl on 2 separate analyses, systolic pressure < 140 mmHg and diastolic pressure < 90 mmHg, and non-smoker or < 5 cigarettes/day smoker.

The exclusion criteria were: contraindications to iodinated contrast agent administration, pregnancy, regular use of alcohol (> 2 drinks/day), oncological history, family history of vascular disease, transient ischemic attack or stroke in the previous 5 years, and current or past use of intravenous drugs.

The final study group was composed of 47 psoriatic patients (patient group: 26 males and 21 females, aged 35-70 years), without conventional cardiovascular risk factors, and an equal number of non-psoriatic subjects, who had undergone epiaortic vessel CDUS at the Department of Diagnostic Imaging, recruited retrospectively between January 2017 and July 2017, (control group: 27 males and 20 females, aged 35-70 years). They underwent CDUS as a general exam, and from the medical interview carried out before the US examination it was determined they were in good health with no noteworthy diseases or underlying conditions, and without conventional cardiovascular risk factors.

Among the psoriatic patients, 37 were affected by psoriasis vulgaris and 10 by severe psoriatic arthritis.

Conclusion

Our results highlight that PsO could be considered a predisposing factor for atherosclerotic disease development in epiaortic vessels, as it causes an increased IMT, that is also considered an independent cardiovascular risk factor.

CDUS revealed atheromatous plaques in 4 patients and IMT > 1 mm in 4 ones (overall prevalence of 17%). The difference of atherosclerotic disease prevalence between the groups was statistically significant (P < 0.05).

Conclusion: Our results highlight that PsO could be considered a predisposing factor for atherosclerotic disease development in epiaortic vessels, as it causes an increased IMT, that is also considered an independent cardiovascular risk factor.
them were being treated with systemic drugs including cyclosporine and/or methotrexate and anti-tumor necrosis factor α (TNF-α) biologic drugs. All the subjects gave informed consent prior to their inclusion in the study.

All the subjects underwent epiaortic vessels CDUS. These evaluations were executed with a high-resolution US equipment (Philips iU22 Ultrasound System), using a high-frequency linear probe (9-3 MHz) and a carotid preset. The neck vessels studied were common carotid arteries, internal carotid arteries and external carotid arteries, and we evaluated both side regions of the neck for each subject for a total of 94 common carotid arteries, 94 internal carotid arteries, and 94 external carotid arteries in the psoriatic patients and an equal number of vessels in the non-psoriatic subjects. The vertebral arteries were examined in all participants, but the results obtained were not included in the study.

The US examinations were carried out by a radiologist with 5 years of experience, and the images were evaluated in consensus with a radiologist with 25 years of experience. The US exams were performed at first in B-mode with axial and longitudinal scans in order to identify arterial wall intima-media thickness (IMT) of common carotid arteries and the presence of common and internal carotid plaques.

The IMT measurement was performed automatically with dedicated software. The mean value between left and right sides was taken into consideration and an IMT <1 mm was considered normal. The presence of a plaque was considered when a focal IMT was greater than 50% of the surrounding area [15]. Subsequently CDUS, and pulsed Doppler spectral analysis were performed: peak systolic velocity (PSV cm/s) and end diastolic velocity (EDV cm/s) values were analyzed to determine the percentage of stenosis and plaque hemodynamics.

When at least 1 carotid plaque or an increased IMT of the common carotid on a side was detected with US examination, the patient was considered positive for atherosclerotic disease. If both carotids had an IMT >1 mm, the average thickness of the 2 was taken into consideration.

In the psoriatic patient group, if CDUS examination detected atherosclerotic plaque, the patient had to go simultaneous CTA of the extracranial vessels in order to confirm its presence, better define plaque features, determine the percentage of stenosis, and search for the presence of additional plaques in other locations. Psoriatic patients who at CDUS presented an IMT >1 mm were asked to follow-up after 12 months with another CDUS to check for vascular disease. The psoriatic patients who did not present any atherosclerotic pathology at CDUS were asked to follow-up with regular dermatological visits.

Subjects of the control group underwent epiaortic vessel CDUS. If a plaque revealed severe stenosis (> 70%) or if signs of surface ulceration were detected, they underwent a CTA to ensure adequate therapeutic diagnostic planning of the incidental finding, according to the current clinical practice. The CTA was performed using a Lightspeed VCT 64-slice scanner (General Electric), with a pre-contrast phase and an arterial phase with bolus tracking, with a non-ionic iodinated contrast agent injection (350 mg/ml) with a flow rate of 3.5 ml/s, followed by a bolus of 20 ml of saline flush at the same speed. The images were also analyzed in 3D, with multiplanar reconstruction and volume rendering and interpreted in consensus with the same two radiologists. When a plaque was detected, the carotid stenosis was quantified by the NASCET method: (distal diameter of the internal carotid – residual diameter / distal diameter of the internal carotid) x100 [16]. The radiological features of the detected plaques analyzed with CDUS and CTA were the percentage of stenosis, structure, and surface.

Continuous variables, normally distributed (patient age, IMT thickness) were presented as the mean ± standard deviation (SD) and categorical variables were presented as counts (percentage). Fisher exact test was used to compare differences in atherosclerotic disease prevalence between psoriatic patients and healthy subjects. Any P value < 0.05 was considered statistically significant.

Results

The mean (SD) age of the psoriatic group was 50.9 ± 8 years (range 35-70 years), and of the control group 51.3 ± 8 years (range 35-70 years). In the psoriatic patients an IMT >1 mm without carotid plaques (Figure 1) was found in 12 patients (25.5%), with a mean value of 1.4 mm (range 1.1-1.8 mm). Atheromatous plaques were found in 6 patients, mean age 57.5 ± 4.6 years (range 50-64 years), with a prevalence of 12.7%. In 4 patients, an increase of IMT coexisted, thus the

Figure 1. Longitudinal US of the right common carotid artery of a 51-year-old female psoriatic patient with an IMT > 1 mm without plaque. IMT = intima-media thickness; US = ultrasonography.
increase of IMT was detected in a total of 16 patients with a prevalence of 34%. A total number of 18 patients showed carotid atherosclerotic disease with an overall prevalence of 38.2%.

Plaques were found in 6 patients and were localized in carotid arteries bilaterally in each patient, with a total number of 12 plaques. Among these, US revealed 2 plaques located in internal carotid artery (ICA), 4 plaques located in carotid bifurcations, and 6 plaques located in carotid bifurcations extended to the ipsilateral ICA. Moreover, the structure of the plaques was hypoechoic in 4 cases (33%) and fibrocalcific in 8 cases (67%). The plaque surface was smooth (83.4%) or irregular (16.6%), no ulceration signs were detected at US examination. In these 12 cases the plaques revealed mild stenosis, with a percentage of stenosis variable at 10-30%. Pulsed Doppler spectral analysis consistently showed a PSV < 125 cm/s with an EDV < 40 cm/s in the ICA, demonstrating that the stenosis was not hemodynamically significant (Figure 2).

All plaques detected with CDUS analysis were confirmed with CTA examination (Figure 3). At the final CTA, 4 plaques were in a left bifurcation and ICA (33.3%), 3 plaques were in a right bifurcation and ICA (25%), 2 plaques were in a...
right bifurcation (16.6%), 1 in a left bifurcation (8.3%), 1 in a right ICA (8.3%) and 1 in a left ICA (8.3%); 8 plaques were fibrocalcific (67%), 2 hypoechoic plaques which were previously documented at US showed a wide fibrous cap (16.5%), and 2 were lipid-rich plaques (16.5%) (Table 1). All of them produced a stenosis < 30% and none of them showed features of vulnerable plaques following both CDUS and CTA examinations. Our results showed good agreement between the two imaging techniques, with a concordance rate of 92% between CDUS and CTA regarding plaque localization, 83% regarding plaque structure, and 100% regarding both percentage of stenosis and plaque surface morphology.

Figure 3. (A) Axial ultrasound of a fibrocalcific plaque in left internal carotid artery of a 58-year-old male psoriatic patient, with a smooth surface that produced stenosis of about 20%. (B) Oblique reconstruction of computed tomography angiography of the plaque that produced a stenosis of about 20%.

### Table 1. Epidemiological Characteristics of Psoriatic Patients with Plaques (n = 6) and Features of These Plaques (n = 12) With CDUS and CTA Examinations*

<table>
<thead>
<tr>
<th>Psoriatic Patient</th>
<th>Technique</th>
<th>Location</th>
<th>Stenosis</th>
<th>Structure</th>
<th>Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, 60 years</td>
<td>CDUS</td>
<td>Right bifurcation + ICA</td>
<td>30%</td>
<td>Fibrocalcific</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Right bifurcation + ICA</td>
<td>30%</td>
<td>Fibrocalcific</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td>CDUS</td>
<td>Left bifurcation + ICA</td>
<td>30%</td>
<td>Fibrocalcific</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Left bifurcation + ICA</td>
<td>30%</td>
<td>Fibrocalcific</td>
<td>Irregular</td>
</tr>
<tr>
<td>Male, 50 years</td>
<td>CDUS</td>
<td>Right ICA</td>
<td>25%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Right ICA</td>
<td>25%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CDUS</td>
<td>Left bifurcation + ICA</td>
<td>20%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Left bifurcation + ICA</td>
<td>20%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td>Male, 58 years</td>
<td>CDUS</td>
<td>Right bifurcation</td>
<td>15%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Right bifurcation</td>
<td>15%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CDUS</td>
<td>Left ICA</td>
<td>20%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Left ICA</td>
<td>20%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td>Female, 64 years</td>
<td>CDUS</td>
<td>Right bifurcation + ICA</td>
<td>30%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Right bifurcation + ICA</td>
<td>30%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CDUS</td>
<td>Left bifurcation</td>
<td>20%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Left bifurcation + ICA</td>
<td>20%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td>Female, 57 years</td>
<td>CDUS</td>
<td>Right bifurcation</td>
<td>20%</td>
<td>Fibrous + lipid core</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Right bifurcation</td>
<td>20%</td>
<td>Fibrous + lipid core</td>
<td>Irregular</td>
</tr>
<tr>
<td></td>
<td>CDUS</td>
<td>Left bifurcation + ICA</td>
<td>10%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Left bifurcation + ICA</td>
<td>10%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td>Female, 56 years</td>
<td>CDUS</td>
<td>Right bifurcation + ICA</td>
<td>15%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Right bifurcation + ICA</td>
<td>15%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CDUS</td>
<td>Left bifurcation</td>
<td>20%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>CTA</td>
<td>Left bifurcation</td>
<td>20%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
</tbody>
</table>

*CDUS errors compared to CTA are highlighted in gray.
CDUS = color Doppler ultrasonography; CTA = computed tomography angiography; ICA = internal carotid artery.
Moreover, CTA did not reveal the presence of additional plaques along the carotid axes or along vertebral arteries.

Regarding subjects of the control group, US examination revealed IMT > 1 mm without carotid atheromatous plaques in 4 people (8.5%) bilateral or unilateral, with a mean value of 1.2 mm (range 1.1-1.5). Atheromatous plaques were detected in 4 subjects, mean age 62.5 ± 2.6 years (range 59-64), with a prevalence of 8.5%. Plaques were unilateral in 2 cases and bilateral in 2 cases, with a total number of 6 plaques. The structure of these plaques was hypoechoic in 2 cases (33.3%), and fibrocalcific in 4 cases (66.7%), with a variable percentage of stenosis at 10-20%, and none of them were hemodynamically significant at color Doppler analysis. Other plaque features of the control group subjects are explained in Table 2.

In 2 cases an increased IMT coexisted, thus an increased IMT was detected in a total of 6 subjects with a prevalence of 12.7%. A total number of 8 cases showed carotid atherosclerotic disease with an overall prevalence of 17%. The Fisher exact test statistic value was 0.0368, and this result highlights the presence of a statistically significant difference (P < 0.05) between the prevalence of carotid atherosclerotic disease (increase of IMT and/or atheromatous plaques) in patients without cardiovascular risk factors affected by PsO and those without cardiovascular risk factors and without PsO.

**Conclusions**

PsO is a chronic systemic inflammatory disease. With the term “psoriasis march,” Boehncke et al described the process that starts from genetic and environmental predisposing factors and leads to a dysregulation of the immune system that gives rise to a chronic systemic inflammatory state that also causes endothelial dysfunction, atherosclerosis, and coronary events. Innate and adaptive immune systems are likewise considered responsible for pathological changes in both epidermis and vascular walls [2].

A recent meta-analysis of 4 genome-wide association studies selected a broad number of single nucleotide polymorphisms (SNPs) that showed a significant association with cardiovascular disease, hypertension, body mass index, hyperlipidemia, or type II diabetes. They then investigated which one of these polymorphisms was also associated with PsO [17] and identified 8 main SNPs codifying for a key protein in the process of lymphocyte differentiation, thrombogenesis, and in the induction of VCAM1 and E-selectin on the surface of endothelial cells under the stimulation of TNF-α. This might explain its dual role in establishing a susceptibility to multiple immune-mediated and cardiovascular diseases. Subcutaneous tissue is able to produce proinflammatory cytokines and C-reactive protein under the influence of mediators such as TNF-α [18].

Modifications in the adipocyte metabolic profile, including alterations of adiponectin, leptin and resistin, are considered responsible in starting or maintaining the inflammatory process [19]. In particular, high blood levels of resistin seem to be related to a proinflammatory systemic state, insulin-resistance, and atherosclerosis [2].

Metabolic syndrome is more frequent in psoriatic patients than in the general population [12], and its prevalence directly correlates to PsO duration and severity [20]. Of note, the abovementioned effects are particularly relevant when dealing with central or visceral obesity [21]. A direct correlation between severity of PsO, central obesity and vascular inflammation has been reported, with concurrent reduction of these parameters after 12 months of systemic or biologic therapy [22].

**Table 2. Epidemiological Characteristics of Non-Psoriatic Patients (n = 8) with Atheromatous Pathology (IMT >1 mm and/or plaques) and Features of the Plaques (n=6) Detected With CDUS**

<table>
<thead>
<tr>
<th>Non-Psoriatic Subjects</th>
<th>Location</th>
<th>Pathology</th>
<th>Stenosis</th>
<th>Structure</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, 64 years</td>
<td>Right bifurcation</td>
<td>Plaque</td>
<td>15%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>Left bifurcation</td>
<td>Plaque</td>
<td>20%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>IMT 1.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male, 65 years</td>
<td>Right bifurcation + ICA</td>
<td>Plaque</td>
<td>20%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td>Male, 59 years</td>
<td>Left bifurcation + ICA</td>
<td>Plaque</td>
<td>10%</td>
<td>Lipid-rich</td>
<td>Smooth</td>
</tr>
<tr>
<td>Female, 62 years</td>
<td>Left bifurcation</td>
<td>Plaque</td>
<td>15%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>Right bifurcation + ICA</td>
<td>Plaque</td>
<td>15%</td>
<td>Fibrocalcific</td>
<td>Smooth</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>IMT 1.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female, 61 years</td>
<td>Right</td>
<td>IMT 1.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male, 68 years</td>
<td>Bilateral</td>
<td>IMT 1.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male, 61 years</td>
<td>Left</td>
<td>IMT 1.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female, 62 years</td>
<td>Bilateral</td>
<td>IMT 1.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CDUS = color Doppler ultrasonography; ICA = internal carotid artery; IMT = intima-media thickness.
Recently, sonoelastography has been proposed as a tool in monitoring the response to treatment in psoriatic patients, as it evaluates hypodermal adipose tissue inflammation underneath lesioned plaques at baseline and during systemic treatment [23].

Twenty-five years ago, McDonald and Calabresi performed the first study showing that patients with PsO had more vascular occlusive events than patients without PsO [3]. Subsequently, multiple studies confirmed the association between moderate-severe PsO and atherosclerosis, coronary artery calcification, higher cardiovascular risk, myocardial infarction, stroke and peripheral vascular disease [4-11]. It is hypothesized that this association might be due to an overrepresentation in the psoriatic population with a Framingham Risk Score (age, hypertension, obesity, smoking, diabetes, hypercholesterolemia, hyperlipidemia, and familial history) [12]. In addition, many traditional systemic therapies for PsO seem to affect cardiovascular risk, increasing cardiovascular risk factors such as hyperlipidemia, hypertension, and hyperhomocysteinemia. Nevertheless, recent studies identified PsO as an independent risk factor for cardiovascular disease [9,10,11,12,13,20].

An increased prevalence and severity of coronary artery calcification and atherosclerosis (measured by cardiac computed tomography, CTA, or coronary angiography) has been reported in psoriatic patients compared to healthy controls [24-30]. A lower coronary flow reserve has been observed in young subjects, otherwise healthy patients with severe PsO compared to controls, suggesting that early impairment of coronary microvascular function is independent of conventional cardiovascular risk factors.

Our study reveals abnormalities in the vessel walls of carotid arteries in a great percentage of psoriatic patients who did not have any cardiovascular risk factors. In particular, we highlighted a higher prevalence of carotid atherosclerotic disease (increased IMT and/or atheromatous plaques) in patients affected by PsO than in healthy subjects regardless of cardiovascular risk factors. It was detected in an increased IMT, which represents a predisposing risk factor for stroke events [31]. Analysis of the data also showed a higher mean age in the control group affected by atheromatous disease and, especially, for detection of occlusive disease [32]. This means that CDUS should not be replaced as the first-line investigation for epiaortic vessels.

Although our results are based on a small cohort of patients, we concluded that PsO could be considered a risk factor for the development of atheromatous pathology in epiaortic vessels, because primarily it causes a thickening of the IMT. Therefore, this study contributes to support the hypothesis that PsO should be considered as an independent cardiovascular risk factor.

The American Society of Echocardiography more recently recommended the cut-off value for IMT at ≥ 1.5 mm, but set IMT above 1 mm [15]. The main limitation of this study is the small cohort of subjects included and, in this regard, further studies with larger cohorts, carried on in close cooperation with different medical specialists, finalized to a correct selection of patients, are necessary to confirm and improve our results. This could be relevant in order to aid in the clinical management of psoriatic patients and offer them better diagnostic/therapeutic pathways to prevent cardiovascular disease.

We propose that epiaortic CDUS as the most suitable method in assessing cardiovascular risk and in the early identification of minor changes and atheromatous plaques of epiaortic vessels of psoriatic patients.

References


30. Eckert J, Schmidt M,Mage dadoz A, Voigtlander T, Schmermund A. Coronary CT angiography in managing atherosclerosis. Int J Mol...

Collagen Supplements for Aging and Wrinkles: A Paradigm Shift in the Fields of Dermatology and Cosmetics

Hend Al-Atif

1 College of Medicine, King Khalid University, Saudi Arabia

Key words: aging, oral collagen, topical collagen, collagen supplements, wrinkling


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Corresponding author: Hend Al-Atif, College of Medicine, King Khalid University, Saudi Arabia. E-mail: hmsalatif@yahoo.com

ABSTRACT

Introduction: Slowing the aging process by use of collagen supplements has become a driving force in the field of dermatology and cosmetics. Generally, oral and topical collagen are used in anti-aging products, as reported in the literature.

Objectives: The overarching goal of this research is to collate the consequences of oral collagen with those of topical collagen in reducing or delaying the aging process.

Methods: We executed an electronic search in Google Scholar and PubMed. We considered a study eligible if it was original research, published in English between 2010 and 2020, and if it provided information on the topic of collagen and aging. We retrieved 12 full-text articles, and these were assessed by reviewers independently.

Results: All human studies included in the review were randomized controlled trials mainly conducted in high- to middle-income countries which highlighted that both oral and topical collagen supplements help to delay the aging process, with no differences arising between the two types of collagen. The evidence from the reviewed studies suggested that both collagen supplements improve skin moisture, elasticity, and hydration when orally administered. Additionally, collagen reduces the wrinkling and roughness of the skin, and existing studies have not found any side effects of its oral supplements.

Conclusions: Both oral and topical collagen can contribute to reducing or delaying skin aging. Future epidemiological studies with large sample sizes and thorough follow-up measures would be required to comprehensively understand the potential effects of these two types of collagen on the aging process.
Introduction

Aging of the skin is a continuous process related to a depletion in the physiological function of the skin [1]. Both natural and unnatural factors cause human beings and animals to experience physiological alterations in different organs as time passes [2]. Cutaneous aging is a multifactorial activity dependent on both inherent (genetic, hormonal, and metabolic), and extrinsic factors (perennial exposure to UV rays, smoking, air pollution, chemicals and poor nutrition) [3,4]. Aging has a detrimental effect on connective tissue in the skin, leading to declines in elastin and collagen fibers and thus resulting in fine lines and wrinkles [3]. Furthermore, aging reduces the production of proteoglycans and glycosaminoglycan (such as hyaluronic acid) in the skin, as well as cartilage [4]. As a result, skin tissue weakens, losing its integrity, and the skin becomes dry, unable to retain enough moisture. Although multiple intrinsic processes can affect the aging process, factors such as exposure to sun, liquid intake, lifestyle, and pollution can exacerbate the aging process [1]. Moreover, skin wrinkling also progresses as dermal thickness is reduced over time due to decreased collagen [5,6].

Most of the collagen supplements recommended by experts are enriched with peptides containing amino acids - including proline, glycine, and hydroxyproline - considered to be essential components of collagen [7-9]. Beyond this, researchers have claimed that increasing peptide production of hyaluronic acid in skin fibroblasts induces fibroblast migration and strengthens collagen, thus raising the amount of moisture in the stratum corneum [10]. Hence, the existing data suggest that the presence of these proteins in the body helps to maintain the amount of collagen in the skin [10]. Furthermore, collagen is considered crucial for skin health because both photo-aging and intrinsic aging decrease its presence in the body [11]. This in turn causes a decrease in the skin thickness, as well as a loss of elasticity and flexibility [12].

In recent years, collagen supplements have been increasingly used, as they are advertised as a potential remedy against the aging process [13]. It has been found that marine fish collagen has homology with human collagen and therefore it has been widely utilized as nutritional addendum along with collagen peptides [14]: they have a very good safety profile, biocompatibility, high bioavailability in the human gastrointestinal barrier, safety, and high bioactivity [15].

Objectives

Current research reveals that collagen use could result in a reduction of wrinkles, rejuvenation of skin, and reversal of skin aging [16], which may improve skin hydration and elasticity [17]. However, the available evidence regarding types of collagen or its mechanism of action, duration to produce desired results and side effects have not been rigorously reviewed or synthesized. This could create controversy in using collagen to reverse the aging process. Moreover, it is yet unclear which type of collagen (topical or oral) needs to be used to produce these coveted effects. Therefore, we undertook this research to collate the consequences of oral collagen with those of topical collagen in reducing or delaying the aging process.

Methods

The researcher conducted this research to appraise, synthesize, and aggregate the available evidence to measure how both oral and topical collagen are used to reduce or delay the aging process.

Inclusion and Exclusion Criteria

The researcher carried out an electronic search on different attributes of collagen, such as the benefits of collagen supplements, types, mechanisms of action, and side effects, as well as how long it takes to produce results. Study inclusion eligibility was contingent on whether the research had focused the effects of collagen supplements on aging reversal and whether it was an original study published in English from 2010 to 2020 across both developed and developing countries. The researcher excluded secondary data, letters to the editor, case reports, and gray literature from this review.

Information Sources and Search Strategy

The research was conducted by the researcher who completed a search of published articles in 2020, scanning databases such as PubMed and Google Scholar. An independent search was carried out by the author, who examined the results for potentially appropriate studies, retrieving any needed full-text articles. The researcher grouped search terms into 4 major categories by PICOS (Population, Intervention, Comparison, Outcomes and Study) design as a framework to formulate eligibility criteria. The researcher identified a combination of Medical Subject Heading (MeSH) keywords and text words. The most prevalent search terms found in abstracts and titles included the following: “collagen supplement and aging,” “collagen supplement and wrinkles,” “role of collagen supplement in skin rejuvenation,” “collagen supplement and aging reversal,” “benefits of collagen supplements in reducing aging,” “types of collagen in reducing aging,” “mechanism of collagen supplements in reducing aging” and “side effects of collagen supplements used for anti-aging”.

Data Extraction

All appropriate research studies were imported into the reference manager software (Endnote, Clarivate Analytics) file, where each study was reviewed, and titles were also screened for duplicates. The abstracts were not considered for further
review, which did not explicitly explore the study objective. Finally, the full-text articles of the remaining germane articles were obtained and examined. This action was followed by abstracting and summarizing the articles that met the eligibility criteria using a proforma standard. Aside from this, the bibliography of the remaining studies was scrutinized to avoid missing any useful studies. This process of searching the articles was carried out independently by the author, and their judgments and extracted summaries were matched to identify the differences and to resolve them accordingly.

Independent reviewers filled out a standardized data extraction sheet for the eligible research articles. The reviewers compared the data extraction tables to ensure including the imperative findings of the eligible studies and pilot tested these sheets before beginning the extraction process. Besides, prevailing research articles on the chosen topic were reviewed to describe the data extraction proforma objectives. Any discrepancies between the independent reviewers were resolved by consensus between two other reviewers.

**Results**

**Decisions Reached Regarding the Search Strategy**

The researcher screened the identified articles initially by titles, then by abstracts, and finally, a full-text article assessment was carried out, discarding any articles not meeting the pre-defined eligibility criteria. As a result, the initial search identified 820 citations in PubMed and Google Scholar; however, 150 articles were duplicates. Of the remaining 670 unique studies, the researcher reviewed titles and abstracts, finding 150 relevant abstracts. Upon reviewing the latter, 135 articles did not meet the eligibility criteria. Hence, the researcher was able to retrieve the complete texts of 15 articles, though more than 12 articles met the necessary criteria and were included in the review, as shown in Figure 1.

**Usage of Oral Collagen Supplements: Evidence from Human Studies**

A study was conducted in Japan in which authors gave collagen peptides to patients with aging, wrinkled skin (Table 1). These patients included 66 women from Japan who were more than 40 years old, about whom researchers recorded any improvements in skin parameters. These patients were given either 10 g of collagen for 56 continuous days or no treatment at all (placebo) [18]. The authors observed a statistically noteworthy dissimilarity in the moisture of the skin throughout the experiment, accompanied by a substantial increase in the moisture for the group under treatment when compared with the placebo group. Skin moisture analyzers were utilized to test skin moisture; they are portable devices that test different skin factors utilizing

![Figure 1. Flow chart summarizing the identification and selection of papers.](image-url)
bioelectric impedance analysis. The level of skin moisture is ascertained by the time it takes for the current to travel across the skin. Additionally, the same study enrolled French women of more than 40 years old and followed a similar protocol for collagen treatment for about 3 continuous months. At the completion of treatment, the author found a noteworthy moisture elevation in the collagen treatment group compared with the placebo group [18].

Moving forward, researchers undertook a randomized controlled trial (RCT) in order to evaluate the potency of collagen peptides [19]. Recruited participants were randomly assigned to ingest either oral liquid supplements containing collagen peptides (50 ml) or placebo daily for 12 weeks [19]. No noteworthy dissimilarity in skin elasticity was noticed between the 2 arms (Table 1). However, in the subgroup analysis, the authors noticed that study participants who underwent cosmetic surgeries in the treatment group showed improvement in skin elasticity, as opposed to their counterparts, who showed no improvement. At the completion of the study, participants in the therapeutic arm achieved higher marks in some skin parameters like hydration and elasticity [19].

In another RCT, women were allocated to 4 different arms [20]. The first arm received 2.5 grams of collagen hydrolysate, the second arm was given 5.0 grams of collagen hydrolysate, the third arm received 2.5 grams of a placebo, and the fourth arm was given 5.0 grams of placebo [20]. Participants were followed for around 60 days, and it was found that each treatment arm with a different dose of collagen hydrolysate showed a statistically noteworthy rise in the elasticity of the skin when juxtaposed with their counterparts in 2 placebo groups. Improvement in elasticity was noticed among elderly women relatively earlier (ie, at 1-month follow-up) [20]. Furthermore, a positive correlation was observed between treatment with collagen hydrolysate and skin moisture and evaporation, with statistically insignificant results [20].

Another double-blinded RCT was undertaken to assess the collagen (with low molecular weight) effects on the elasticity of the skin elasticity, hydration, and finally wrinkling [21]. This study was conducted with Korean women at least 40 years old (n = 64) who were randomized to 1000 mg of collagen or to placebo every day for 3 months [21]. The authors found noteworthy elevations in skin hydration in the treatment group compared with the placebo group, as shown in Table 1 [22]. The study was comprised of 3 main groups: 1 was randomized to receive collagen peptides (higher content), 1 was randomized to collagen peptides (lower content), and the last group received placebo [22]. The total duration of the study was roughly 2 months, and participants took their respective treatments daily. Both intervention arms demonstrated substantial improvement in skin moisture, especially around the cheek and canthus, as opposed to the placebo group, which displayed no such improvements. Moreover, the findings also showed a substantial increase in the moisture and elasticity of the skin, as well as a reduction in wrinkling and roughness in the first treatment group, unlike either the second or the placebo groups, as shown in Table 1 [22].

Usage of Oral Collagen Supplements: Evidence from Animal Studies

Apart from studies conducted on human beings, animals have been examined as well to assess the effect of collagen [23]. In animal models, the authors have used clinical and histological appearance, along with gene expression, to study the necessary outcomes. One research was carried out to assess the consequences of collagen hydrolysates on 9-month-old mice for 24 weeks. The results of the study revealed a significant increase in both distribution and density of said collagen and ratio between type I and type III collagen, with a particular dose-response relationship [23].

In another study, collagen peptides were given to mice for one and a half months [24]. The authors found a higher expression of genes, along with their upregulation in the skin [24]. One more study was conducted on mice, in which they were fed a diet containing collagen hydrolysate for roughly 3 months. The study revealed improvements in the water content of their skin and an increase in elasticity, as opposed to the mice in the control group, who experienced no such benefits [25]. Lastly, mice were observed on a diet rich in prolylhydroxyproline and hydroxypropylglycine for around 5 weeks in one more study. The mice that received collagen hydrolysates showed increased skin hydration [26].

Usage of Topical Collagen Application on Delaying the Aging Process

Generally, there have been fewer studies assessing the effect of topical collagen on the aging process when compared with the studies conducted for oral collagen supplements. For instance, one conducted by Sanz et al in 2015 revealed that those women who were asked to apply a product containing collagen performed better than those in the control group [27]. More specifically, around three quarters of the treated women showed anti-wrinkling effects and substantial increases in the dermal density and elasticity of their skin after 7 days of treatment [27]. Similarly, Matthias et al conducted a retrospective study in Germany and South Africa on 480
### Table 1. Previous usage of Oral Collagen Supplements: Evidence from Human Studies

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Study Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Participants</th>
<th>Age (Years)</th>
<th>Intervention</th>
<th>Control Arm</th>
<th>Study Results</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangsuwan et al [40]</td>
<td>2020</td>
<td>Thailand</td>
<td>RCT</td>
<td>36</td>
<td>Post-menopausal women</td>
<td>50-60</td>
<td>5 grams of oral collagen hydrolysate</td>
<td>Placebo</td>
<td>Skin elasticity was found to be significantly different between intervention and control groups.</td>
<td>None</td>
</tr>
<tr>
<td>Žmitek et al [39]</td>
<td>2020</td>
<td>Germany</td>
<td>RCT</td>
<td>34</td>
<td>Caucasian Healthy females</td>
<td>40–65</td>
<td>10 mL of a syrup having fish collagen and other active ingredients</td>
<td>Placebo</td>
<td>Dermis density was improved. Periorbital wrinkle area was reduced. Improvement in skin smoothness. Skin hydration improved. Dermis thickness, trans-epidermal water loss and viscoelasticity did not improve.</td>
<td>None</td>
</tr>
<tr>
<td>Campos et al [29]</td>
<td>2019</td>
<td>RCT</td>
<td>60</td>
<td>Healthy study participants</td>
<td>40-50</td>
<td>Topical and hydrolyzed collagen</td>
<td>Placebo in oral form</td>
<td>- Topical collagen improved skin elasticity and viscoelasticity parameters. - Skin elasticity, hydration and echogenicity of dermis were improved after 1 month of topical collagen application, as well as oral collagen.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Bolke et al [41]</td>
<td>2019</td>
<td>Germany</td>
<td>RCT</td>
<td>72</td>
<td>Healthy females</td>
<td>≥ 35</td>
<td>2.5 grams of collagen and other active ingredients</td>
<td>Placebo</td>
<td>- Hydration of skin, elasticity and density were improved. - There was reduction in skin roughness. - All test parameters were different between intervention and placebo groups, which also remained at the time of follow-up.</td>
<td>None</td>
</tr>
<tr>
<td>Kim et al [21]</td>
<td>2018</td>
<td>Korea</td>
<td>RCT</td>
<td>64</td>
<td>Korean women</td>
<td>40–60</td>
<td>Collagen with low molecular weight</td>
<td>Placebo</td>
<td>- The intervention group showed improvement in the hydration values of skin at 6 and 12 weeks. - Three parameters of skin wrinkling improved drastically in the intervention, as opposed to the placebo. - 1/3 parameters improved substantially in the intervention group after 12 weeks as opposed to placebo group. - 2/3 parameters in the intervention arm improved after 12 weeks.</td>
<td>None</td>
</tr>
</tbody>
</table>
Table 1. Previous usage of Oral Collagen Supplements: Evidence from Human Studies (continued)

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Study Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Participants</th>
<th>Age (Years)</th>
<th>Intervention</th>
<th>Control Arm</th>
<th>Study Results</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoue et al [22]</td>
<td>2017</td>
<td>China</td>
<td>RCT</td>
<td>85</td>
<td>Chinese women</td>
<td>35–55</td>
<td>Collagen hydrolysate having a higher content of bioactive collagen-Collagen hydrolysate having a lower content of bioactive collagen</td>
<td>Placebo</td>
<td>- The intervention arm demonstrated a significant improvement over the placebo arm in moisture, elasticity, wrinkles, and roughness.</td>
<td>None</td>
</tr>
<tr>
<td>Genovese et al [19]</td>
<td>2017</td>
<td>Rome (Italy)</td>
<td>RCT</td>
<td>120</td>
<td>Volunteer subjects</td>
<td>47.72 (6.5) 49.65 (6.5)</td>
<td>50 mL of collagen</td>
<td>Placebo</td>
<td>- No difference was seen between the intervention and placebo arms for skin elasticity. - Subjects who had cosmetic surgeries demonstrated increased skin elasticity.</td>
<td>None</td>
</tr>
<tr>
<td>Sanz et al [27]</td>
<td>2015</td>
<td>Spain</td>
<td>Open and intra-individual study clinical study</td>
<td>32 women</td>
<td>Women with sensitive skin bearing wrinkles</td>
<td>45-55 (median: 49)</td>
<td>Serum containing an amalgamation of pro-collagen lipopeptide, extract of apple, creatine, and urea</td>
<td>Self-control</td>
<td>- 71% of the women in the intervention group experienced anti-wrinkle effects. - Dermal density improved by 11% after 1 week. - Significant improvement was seen in cutaneous hydration and cutaneous elasticity (cheekbone) after 1 week when compared with baseline.</td>
<td>No adverse events</td>
</tr>
<tr>
<td>Asserin et al [42]</td>
<td>2015</td>
<td>Japan and France</td>
<td>RCT</td>
<td>66</td>
<td>Japanese and French women</td>
<td>40-59 40-65</td>
<td>10 g of collagen</td>
<td>Placebo</td>
<td>- Significant improvement in skin hydration and dermis density after 8 weeks of intake - A significant reduction was seen in the fragmentation of the dermal collagen network.</td>
<td>None</td>
</tr>
<tr>
<td>Proksch et al [20]</td>
<td>2013</td>
<td>Not reported</td>
<td>RCT</td>
<td>69</td>
<td>women</td>
<td>35-55 years old</td>
<td>2.5 g of CH, and 5.0 g of CH</td>
<td>Placebo</td>
<td>- A significant improvement was seen in elasticity of skin in both intervention arms, as compared to the placebo arm. - Elderly women showed a statistically significantly higher skin elasticity level. - No effect of CH was seen on skin hydration and evaporation.</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 1 continues
### Table 1. Previous usage of Oral Collagen Supplements: Evidence from Human Studies (continued)

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Study Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Participants</th>
<th>Age (Years)</th>
<th>Intervention</th>
<th>Control Arm</th>
<th>Study Results</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Byrne et al [30]   | 2010       | Ireland     | RCT                | 22          | Caucasian female subjects   | 39 to 60    | Triple peptide complex (3%)         | Placebo      | - There was substantial reduction in the frequency of wrinkles, total wrinkle surface average, wrinkle length and average wrinkle depth in the intervention group, as opposed to placebo group.  
  - There was improvement in the wrinkle parameters by 10–19% compared with the untreated baseline, and this improvement was 13–28% when compared to the placebo group. | None            |
| Aust et al [28]    | 2008       | Germany     | Retrospective analysis | 480 F: 400 M: 80 | Patients                    | The mean (SD) was 49 ± 15.5 years | Percutaneous collagen | Self-control | - There was improvement in the skin by 60 to 80%.  
  - A substantial upsurge in collagen and elastin deposition on histological examination was observed in the subset of patients.  
  - There was a roughly 40% thickening of the epidermis mainly stratum spinosum after 1 year of treatment. | Not reported    |

CH = collagen hydrolysate; SD = standard deviation; RCT = randomized control trial.
patients with wrinkles, lax skin, scarring, and stretch marks [28]. These patients were administered percutaneous collagen after preparing their skin with necessary vitamins and creams for at least 1 month [28]. The findings demonstrated that patients were found to have skin 60% to 80% improved from before the treatment. Furthermore, researchers carried out a histologic examination on a subset of patients that demonstrated a substantial upsurge in collagen and elastin deposition. There was around 40% thickening of the epidermis, mainly stratum spinosum, 1 year after treatment [28].

Similarly, Campos et al evaluated the consequences of topical and oral collagen additions in the skin enhancement of 60 healthy female subjects. The findings showed that females who were given a topical product demonstrated a substantial rise in skin hydration and elasticity at the end of 1 month. On the other hand, the group with oral supplementation showed more noticeable results in dermal echogenicity and decreasing pore size at the end of 3 months without any adverse effects [29]. Another study demonstrated that those patients who received topical treatment showed a noteworthy depletion in the total wrinkle surface, number of wrinkles, and average wrinkle length and depth were observed in comparison with those who underwent placebo.

In addition, the anti-wrinkle activity of the topical triple peptide complex (3%) has been reported by a clinical research conducted by Byrne et al in 2010. Their findings suggested that topical application significantly improves the photo-damaged skin by the end of 1 month when compared with the placebo group [30]. These studies revealed noteworthy relative depletions in the number of wrinkles and total wrinkle surface - in conjunction with increase in their mean depth and length - at the end of 1 month, ranging from 10% to 28% [30].

**Mechanism of Action of Collagen Supplements**

One of the proteins found in abundance in human beings is collagen, and it helps to maintain the structure, stability, and strength of the dermal layers [31]. The studies have shown antioxidant and established reparative actions of collagen in wrinkled or damaged skin. Skin experiences the double action of collagen: first, it provides the skin essential components for both elastin and collagen, and second, it is attached to the fibroblast receptors in the dermis to initiate the production of elastin and hyaluronic acid [32]. So far, oral collagen has been studied to a greater extent than topical collagen. The available literature suggests that the topical application of collagen improves both skin elasticity and texture. However, topical collagen does not infiltrate the skin completely owning to its high molecular weight [33]. In contrast, oral collagen ingestion has been found to improve mechanical properties by increasing both the density and the diameter of collagen fibrils [34]. Orally consumed collagen bioactive peptides are absorbed relatively quickly because such collagen products have lower molecular weights, distributing these peptides easily across several tissues [35]. Additionally, evidence from the animal models suggested that oral administration of collagen reduces the intensity of skin hydration caused by UV radiation and also reduces hyperplasia of the epidermis caused by UV rays [36]. Furthermore, oral intake of collagen enhances the moisture content of the skin, especially the stratum corneum, as well as the elasticity of the skin, reducing wrinkling and roughness [37]. Overall, collagen causes an increase in fibroblasts and extracellular matrix proteins and a decrease in metalloproteinase. These rising fibroblasts found in the various layers of the human dermis produce a plethora of extracellular matrix proteins that enhance skin health and thus slow skin aging [38].

**Side Effects of Collagen Supplements Reported in Human Studies**

Generally, no adverse effects of oral and topical collagen have been observed in any of these studies [39]. There have been no side effects such as vomiting, diarrhea, nausea, or constipation reported in the treatment or control groups of any of the studies [40]. For example, trials conducted in 2019 and 2020 found no adverse effects of collagen until they observed their participants [39,41]. These findings were also confirmed by a research by Inoue et al in 2017, where they conducted a RCT to assess the effect of high versus low doses of collagen and placebo [22]. Likewise, Genovese et al had shown analogous findings concerning the side effects during the period of study while comparing the effect of supplements on skin elasticity, wrinkling, and roughness with the placebo [19]. Besides, these findings were further endorsed by a study conducted in 2013 by Proksch et al: the authors found no side effects in any of the 4 groups that were assigned to high-dose collagen, low-dose collagen, a high-dose placebo, or a low-dose placebo [20]. One more double-blinded RCT conducted on Korean women showed no adverse events related to the treatment or intervention throughout the study period [21]. Similarly, there were no adverse effects of topical collagen in various studies [28-30].

**Conclusions**

Based on the existing literature from both animal and human studies, it seems that oral collagen supplements improve skin elasticity, turgor, and hydration and reduce skin wrinkling and roughness. The existing premise reveals that neither oral nor topical collagen is superior to the other; rather, both types reduce or delay skin aging. Thus, products of collagen peptides can be considered to be anti-aging remedies by dermatologists, especially in cosmetics. However, the existing evidence has not provided enough robust evidence for collagen...
supplements due to differences in the weights of collagen being topically and systemically absorbed. Hence, more epidemiological and interventional studies with large sample sizes and required follow-up appointments are requested to assess the effectiveness of the topical compounds containing collagen on wrinkled and aging skin while comparing the same to the oral collagen supplement instead of the placebo. As the trend of both forms of collagen supplement use might continue to rise, more thorough research is required to validate their potential positive effects before they are widely used.

One of the strengths of the included studies was research design, as all the studies on human beings were RCTs that provided solid evidence due to the balance of known and unknown confounders between the treatment and control groups. However, the types and doses of collagen were not similar across the studies; therefore, further studies with consistent doses in different settings may be required before making any judgments about the use of oral collagen. This is crucial because some of the proponents of collagen might try to apply the results of animal models to human beings, but animal studies cannot be generalized to humans due to differences in physiological and biological mechanisms. In the same way, these collagen products have usually been tested in the developed or high-income sectors of different age groups. Thus, there is no evidence about whether these products could produce analogous results in the various populations residing in low- to middle-income countries with limited resources. Hence, this warrants the replication of similar studies in developing countries by using a similar study design. Lastly, the review found no side effects of either topical or oral collagen treatment during the study period, and most of the studies had followed their participants for 12-24 weeks. Thus, there is no clear evidence about how these collagen products function after the study ends and whether these products tend to produce adverse effects in the long run that need to be further explored.

References

19. Genovese L, Corbo A, Sibilla S. An insight into the changes in skin texture and properties following dietary intervention with a nutricosmeceutical containing a blend of collagen bioactive peptides


Acne Supplements Sold Online

Emily Burns¹, Milbrey Parke¹, Ariadna Perez-Sanchez², Dina Zamil¹, Rajani Katta³

¹ Baylor College of Medicine, Houston, TX, USA
² Department of Internal Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
³ Department of Dermatology, McGovern Medical School at University of Texas Health Science Center at Houston, Houston, TX, USA

Key words: acne supplement, dietary supplement, diet, nutrition, safety


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Corresponding author: Rajani Katta, MD, Department of Dermatology, McGovern Medical School at University of Texas Health Science Center at Houston, Houston, TX, USA. E-mail: info@kattamd.com

ABSTRACT

Introduction: As no centralized database of acne supplements is available, we aimed to provide an overview of these products, with a focus on safety.

Objectives: The objectives of this study were to document the number, formulation, contents, and marketing strategies utilized by acne supplements sold online.

Methods: An online search was conducted between March and May 2020. Products were included in the study if they used the terms: “whitehead”, “blackhead”, or “acne”. Data were extracted from the website, box, and Supplement Facts label.

Results: 49 products were identified, which contained 146 unique ingredients. These included vitamins, minerals, food extracts, botanical extracts, amino acids, animal products, and distinct microbial strains. Few (4.1%) products were tested by third parties.

Conclusions: This survey of acne supplements available online raised concerns regarding lack of warning labels, teratogenicity, exceedingly large levels of vitamins and minerals, and lack of third-party testing. Given the limited regulation and oversight of dietary supplements, it is imperative that physicians educate patients on the potential risks of these products.
Introduction

Dietary Supplements in the US
Dietary supplements are becoming increasingly popular in the U.S. Studies estimate that approximately 50% of the US population consumes some form of dietary supplement [1]. The number of American people who consume acne supplements is unknown.

The Role of Dietary Supplements in Acne
Acne affects up to 50 million American residents each year, and its prevalence has been reported to be as high as 85% among people aged 12-24 years [2,3]. The role of diet and dietary supplements in the development and treatment of acne is an evolving field of study. A recent systematic review including 53 articles revealed that acne-promoting factors include high glycemic index food, dairy, fatty food, and chocolate. Acne-protective factors include fruits and vegetables. The possible varying degrees of acne-promotion of specific subtypes of these foods (eg full-fat milk vs. low-fat milk) is unknown [4].

High doses of oral zinc have been shown to reduce severe and inflammatory acne in double-blind randomized control trials (RCTs) [5,6]. Successful trials have used different dosages and forms of zinc as well as zinc in combination with other ingredients [7]. Therefore, future research is needed to elucidate the best zinc dose and form associated with improved acne outcomes.

Other vitamins and minerals have been studied, but double-blind RCTs are lacking [5,8]. Low selenium levels have been documented in patients with acne; however, the clinical significance of low selenium and acne development is unknown [5,9]. A cross-sectional study comparing blood levels of vitamins A and E in 100 patients with acne and 100 patients without acne showed that subjects with acne had significantly lower plasma concentrations of these vitamins compared to the control subjects [5,10].

Other naturally occurring compounds have been evaluated in animal and in vitro studies but human studies are lacking. These compounds have exhibited antioxidant and antibacterial properties, such as (--) epigallocatechin-3-gallate from green tea and nobiletin from Citrus depressa (a green citrus fruit native from Taiwan and Japan) [5,11,12]. In hamsters, these compounds have been shown to reduce sebum production and inhibit cell proliferation of sebaceous glands respectively.

The flavonoids kaempferon and quercetin from the Inpatiens balsamina flower as well as resveratrol found in several other plants have been shown to possess antibacterial properties against Propionibacterium acnes in vitro [5,13,14].

Objectives
The objective of this study was to document the number, formulation, contents, and marketing strategies utilized by acne supplements sold online.

Methods
We conducted a search of acne supplements sold online between March 2020 and May 2020 using Google, Amazon, Twitter, and Instagram. Acne supplements were defined as those featuring the words “whitehead”, “blackhead”, and/or “acne” (Figure 1). Data were extracted from the Supplement Facts label, manufacturer website, and/or third-party seller website for each product. Third-party sellers include Amazon and online supplement retailers.

Results

Ingredients
Forty-nine products were identified, which in total contained 146 unique ingredients including vitamins, minerals, food extracts, botanical extracts, amino acids, animal products, and distinct microbial strains (Table 1). Products contained an average of 3.18 vitamins, and the most common vitamins included in descending order were vitamins A, E, B3, B5, and B6 (Table 2). Products contained an average of 2.6 minerals, and the most common minerals included were zinc and selenium (Table 3). Many products contained supraphysiologic doses of vitamins and minerals (Table 4), (Figure 2).
Many products contained botanical and food extracts. The most common extracts included were methylsulfonylmethane (MSM, 20%), coenzyme Q10 (CoQ10,13%), horsetail powder (10%), pepper extract (10%), grape seed extract (8%), turmeric (8%), diindolylmethane (DIM, 7%), and licorice root extract (6%).

**Table 1. List of Selected Ingredients**

<table>
<thead>
<tr>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylsulfonylmethane (MSM)</td>
</tr>
<tr>
<td>Coenzyme Q10 (CoQ10)</td>
</tr>
<tr>
<td>Horsetail powder</td>
</tr>
<tr>
<td>Pepper extract</td>
</tr>
<tr>
<td>Grape seed extract</td>
</tr>
<tr>
<td>Turmeric</td>
</tr>
<tr>
<td>Diindolylmethane (DIM)</td>
</tr>
<tr>
<td>Licorice root extract</td>
</tr>
<tr>
<td>Bovine Adrenal Powder</td>
</tr>
<tr>
<td>Bacteriophages</td>
</tr>
<tr>
<td>Bovine Colostrum</td>
</tr>
</tbody>
</table>

**Table 2. Vitamins Included in Acne Supplements Sold Online**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>% of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>53.1</td>
</tr>
<tr>
<td>B3 (niacin)</td>
<td>34.7</td>
</tr>
<tr>
<td>B5 (pantothenic acid)</td>
<td>34.7</td>
</tr>
<tr>
<td>B6 (pyridoxine)</td>
<td>34.7</td>
</tr>
<tr>
<td>E (tocolpherol)</td>
<td>34.7</td>
</tr>
<tr>
<td>No Vitamins</td>
<td>32.7</td>
</tr>
<tr>
<td>C</td>
<td>30.6</td>
</tr>
<tr>
<td>B7 (biotin)</td>
<td>24.5</td>
</tr>
<tr>
<td>B2 (riboflavin)</td>
<td>16.3</td>
</tr>
<tr>
<td>B12 (cobalamin)</td>
<td>14.3</td>
</tr>
<tr>
<td>D</td>
<td>14.3</td>
</tr>
<tr>
<td>B1 (thiamine)</td>
<td>12.2</td>
</tr>
<tr>
<td>B9 (folate)</td>
<td>10.2</td>
</tr>
<tr>
<td>K</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table 3. Mineral Content (%) of Acne Supplements Sold Online**

<table>
<thead>
<tr>
<th>Mineral</th>
<th>% of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>65.3</td>
</tr>
<tr>
<td>Selenium</td>
<td>40.8</td>
</tr>
<tr>
<td>Chromium</td>
<td>32.7</td>
</tr>
<tr>
<td>Copper</td>
<td>28.6</td>
</tr>
<tr>
<td>Magnesium</td>
<td>28.6</td>
</tr>
<tr>
<td>No Minerals</td>
<td>26.5</td>
</tr>
<tr>
<td>Calcium</td>
<td>14.3</td>
</tr>
<tr>
<td>Manganese</td>
<td>12.2</td>
</tr>
<tr>
<td>Sodium</td>
<td>8.2</td>
</tr>
<tr>
<td>Potassium</td>
<td>8.2</td>
</tr>
<tr>
<td>Iron</td>
<td>6.1</td>
</tr>
<tr>
<td>Sulfur</td>
<td>6.1</td>
</tr>
<tr>
<td>Iodine</td>
<td>4.1</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>4.1</td>
</tr>
</tbody>
</table>

**Table 4. High Doses of Vitamins and Minerals from Selected Acne Supplements**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Labeled Dose</th>
<th>% of Daily Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>21,000 mcg RAE</td>
<td>2,333%</td>
</tr>
<tr>
<td>Vitamin B2 (Riboflavin)</td>
<td>25 mg</td>
<td>1,923%</td>
</tr>
<tr>
<td>Vitamin B3 (Niacin)</td>
<td>500 mg</td>
<td>2,500%</td>
</tr>
<tr>
<td>Vitamin B5 (Pantothenic Acid)</td>
<td>350 mg</td>
<td>3,500%</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>50 mg</td>
<td>2,500%</td>
</tr>
<tr>
<td>Vitamin B7 (Biotin)</td>
<td>7500 mcg</td>
<td>2,500%</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>500 mcg</td>
<td>20,833%</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>280 mg</td>
<td>467%</td>
</tr>
<tr>
<td>Chromium</td>
<td>250 mcg</td>
<td>714%</td>
</tr>
<tr>
<td>Zinc</td>
<td>50 mg</td>
<td>333%</td>
</tr>
</tbody>
</table>

Many products contained botanical and food extracts. The most common extracts included were methylsulfonylmethane (MSM, 20%), coenzyme Q10 (CoQ10,13%), horsetail powder (10%), pepper extract (10%), grape seed extract (8%), turmeric (8%), diindolylmethane (DIM, 7%), and licorice root extract (6%).

**Formulation**

Capsules were the most common formulation, followed by tablets and gummies.
Dosing

47.9% of products did not provide clear labeling for total daily dose. For example, the Supplement Facts box included the dose for one capsule, but the recommended dose is two capsules.

Pricing

Pricing varied from $10-204 per month supply. The median price per month was $31.

Third-Party Seals of Approval

Approximately 4% of products displayed seals of approval from third-party testing centers recognized by the US Office of Dietary Supplements.

Marketing and Claims

The most common marketing claims included gluten free (67%), vegan or vegetarian (45%), made in the USA (43%), natural (43%), hormonal balance or regulates hormones (43%), detoxify (41%), inflammation (39%), antioxidant (37%), proprietary blend (26%), and cruelty free (20%). Most (55.1%) products used the terms “research” or “clinical study” in the marketing materials. Some (8.2%) products cited a clinical study. Most (55.0%) of products had an auto-delivery or subscription option available upon checkout. Most (55.1%) of products had a coupon available upon checkout. Other marketing techniques included before-and-after photographs (51.1%) and video testimonials (12.2%). Most (83.7%) supplements were reviewed on Amazon.

Labeling

Some (20.8%) products had different information provided by multiple sources. In these instances, labels provided by Amazon sellers conflicted with third party sellers and/or manufacturers. For the purposes of the data collection of this study, the label from the manufacturer website was used. Supplement manufacturers are required by law to include the phrase “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease” on the bottle if a structure/function claim is made. 12.2% of products did not have this phrase clearly visible online. A 53.1% of products did not list a phrase containing or similar to “Consult your doctor or health care practitioner before use” and 30.6% of products failed to include any type of pregnancy warning.

Conclusions

Acne supplement manufacturers use a wide variety of ingredients and health claims. There is little consensus among these products regarding the number or dosing of vitamins, minerals, extracts, and other ingredients. They are sold on manufacturer websites and third-party websites. This study raises concerns about lack of US Food and Drug Administration (FDA) oversight, lack of third-party testing, teratogenicity potential, marketing practices, untested ingredient profile, supraphysiologic vitamin dosing, vulnerable patient population, and consumer confusion.

The US FDA regulates supplements as foods, not drugs [15]. There is no requirement to prove safety or efficacy prior to sale, and there is no limit on dosages of vitamins or minerals, even for those with defined tolerable upper limits. There is also no requirement to test or document interactions between ingredients and/or other medications [16].

Although the US FDA requires that supplements sold in stores display the Supplement Facts label, this requirement does not apply to supplements sold online. On some websites, including Amazon and other third-party sellers, this label was not visible.

The FDA has issued Good Manufacturing Practices (GMPs), which are a set of guidelines for safe manufacturing of dietary supplements. The FDA expects manufacturers to comply with GMPs but does not regularly investigate for compliance with these rules [15].

In terms of quality testing, only 4.1% of products in our sample were tested by third-party companies recognized by the Office of Dietary Supplements, including the US Pharmacopeia, National Sanitation Foundation, and Consumer Lab. Without US FDA testing or third-party testing, consumers must rely only on the companies themselves to ensure the safety, purity, and lack of contamination of these products.

To date, there is little data about the quality and safety of acne supplements sold online. Ayurvedic medicines sold online have been documented to contain heavy metals including lead, mercury, and arsenic [17]. In 2015, the New York State attorney general’s office accused four national retailers of selling dietary supplements containing unadvertised, potentially allergenic ingredients. Many products did not contain the advertised herbal ingredients, and some contained allergenic components, such as wheat, while advertising that the product was “gluten-free” [18].

With regards to teratogenicity, prescription medications require a package insert with pregnancy warning categories, which indicate risk to the developing fetus. No such notification is required for supplements, even for compounds that pose a known teratogenic risk. Consumers of child-bearing potential should exercise caution when consuming acne supplements, as some of these products may pose a risk to the developing fetus.

High dietary doses of preformed vitamin A (> 10,000 IU) during early pregnancy are associated with neural crest defects such as cleft lip, ventricular septal defect, transposition of the great vessels, hydrocephalus, and craniosynostosis [19].
In our sample, 6.1% of acne supplements sold online included potentially teratogenic levels of vitamin A. The teratogenic potential of another 8% of products containing vitamin A could not be determined because the products did not specify the form of vitamin A [20].

In terms of marketing strategies, most products (55.1%) included the terms “research” or “clinical study” on the labeling, and some products cited the research used to support the claim. Two studies cited by a product were evaluating magnesium, B6, and a plant extract (Vetex agnes cactus) for use in premenstrual syndrome [21,22]. These studies did not evaluate use of these components for acne. One website referenced three articles that were not found online and could not be substantiated. During the editing process, these articles were removed from the product’s website. Another article did not appear in a PubMed-indexed journal [23].

Our survey documented a wide variety of ingredients contained in these products, including many ingredients that have not been tested in human acne studies. The most included ingredients outside of vitamins and minerals were MSM, CoQ10, horsetail powder, pepper extract, grape seed extract, turmeric, DIM, and licorice root extract. The topical application of grape seed extract is associated with decreased sebum content in human skin [24]; however, we were unable to locate research on oral grapeseed extract intake or the other listed compounds in acne.

Interestingly, the few plant compounds (kaempferon, quercetin, green tea extract and nobiletin) that have been studied in hamsters and in vitro were not the most commonly used extracts. Some unique and unexpected ingredients included bovine adrenal powder, a proprietary enzyme blend including digestive enzymes, bacteriophages intended to affect gut bacteria, and bovine colostrum, intended to improve natural defenses.

High-dose vitamins and minerals were used in multiple products and represent another area of concern. Vitamins A, B2, B3, B5, B6, B7, B12, C as well as chromium and zinc were included in very high doses. As zinc has been shown to reduce acne, it was unsurprising that zinc was the most commonly used mineral (65%) [6].

Supraphysiologic doses of vitamins and minerals included in dietary supplements have been linked to multiple side effects [25]. For example, vitamins B6 and B12 have been associated with a worsening of acne in some reports [26]. Surprisingly, products in our sample included both of these ingredients at high doses: vitamin B6 at 2,500% of Recommended Dietary Allowance (RDA) and vitamin B12 at 20,833% of RDA.

As this analysis focused on products sold online, it highlights dangers posed to a vulnerable pediatric population. Many patients suffering from acne are minors. Anyone, including children, can order acne supplements online. Parents and pediatricians should be wary of these products, as they are readily available online.

Finally, of significant concern is that approximately 1 in 5 (20.8%) supplements sold in multiple outlets (manufacturer, third-party, Amazon) displayed varying doses of ingredients. It is unclear which label consumers should use to evaluate the dose and ingredients included in the supplement.

Limitations

As our study was designed only to investigate products sold online, this represents a limited sample of acne supplements. Further research should evaluate products sold in stores. In addition, the authors could not find any PubMed indexed studies evaluating the components of these products using laboratory testing.

Dietary supplements marketed for acne include supraphysiologic levels of vitamins and minerals as well as food extracts, botanical extracts, amino acids, animal products, and microbes. These products do not require US FDA approval and thus do not undergo the same rigorous safety and efficacy testing as pharmaceuticals; however, most products include the term “research” or “clinical study” on their label. Few products undergo testing by third parties, although they can be pharmacologically active and can be linked to adverse effects. Many of the ingredients included in acne supplements have not undergone RCTs to evaluate their efficacy, and high doses of vitamin A may be associated with birth defects in pregnant patients.

As the US FDA does not routinely monitor supplements sold in stores or online, consumers and physicians reporting is vital for monitoring adverse events. The US FDA has an online Safety Reporting portal, which streamlines the process of reporting product safety issues. The portal may be found here: https://www.safetyreporting.hhs.gov/SP2/en/Home.aspx?id=0506b56b4-2e3-4-0f9-a58b-742b04d74295

References


Evaluation of Dermoscopic Features in Facial Melanosis with Wood Lamp Examination

Bibush Amatya

Key words: facial melanosis, melasma, Wood lamp, dermoscopy

Introduction: Facial melanosis is one of the most common reasons for which patients refer to a dermatologist in Nepal.

Methods: This was a cross-sectional study conducted at the Department of Dermatology and Venereology, Nepal Medical College and Teaching Hospital. We recruited a total of 204 patients from July 2020 to March 2021. The most common diagnosis was melasma (37 patients) followed by melasma with steroid-induced rosacea-like dermatitis (29 patients). After collecting clinical and demographic data, patients underwent Wood lamp and dermoscopic examination.

Results: Dermoscopy of ashy dermatosis and nevus of Ota revealed blue-gray pigmentation forming a curvilinear pattern; café-au-lait macule and nevus spilus revealed a light brown reticular pattern with follicular sparing; and a reticular and hem-like pattern of pigmentation was observed in clofazimine-induced pigmentation, peribuccal pigmentation of Brocq and periorbital pigmentation. The degree of agreement between Wood lamp and dermoscopic findings was found to be statistically significant in melasma (κ = 0.701, P = 0.0001) and melasma with steroid-induced rosacea-like dermatitis (κ = 0.628, P = 0.0001). While the agreement between the two techniques was 100% for epidermal types, it decreased to 44.8% for dermal melasma and 61.5% for dermal melasma with steroid-induced rosacea-like dermatitis.

Conclusions: Dermoscopy is useful in assessing facial melanoses. It may be supplemented with Wood lamp examination to increase diagnostic accuracy.
Introduction

Facial melanoses are characterized by abnormal pigmentation of the face. These disorders include, but are not limited to, ashy dermatosis, discoid lupus erythematosus, ephelides, melasma, melasma with steroid-induced rosacea-like dermatitis, peribuccal pigmentation of Brocq, periorbital hyperpigmentation, postinflammatory hyperpigmentation, and solar lentigo. Also included are various types of nevi, such as Becker nevus, blue nevus, compound nevus, Hori nevus, intradermal nevus, junctional nevus, nevus of Ota, nevus spilus, and verrucous epidermal nevus [1]. Facial melanoses may also present as a result of ingestion of certain drugs like amiodarone, antimalarials, antipsychotics, chloramphenicol, clofazimine, pirfenidone and tetracycline [2].

The diagnosis and differentiation of these conditions are based on history and clinical examination supplemented in some cases by Wood lamp and histopathological evaluation [3]. Dermoscopy is a noninvasive, in vivo technique that allows visualization of the subsurface structures of skin that are normally not visible to the naked eye. Wood lamp examination is another non-invasive technique that helps in the diagnosis of pigmentedary disorders. It uses a specific wavelength light source to distinguish depth of pigmentation depending on different degrees of autofluorescence [4]. There are very few studies that have evaluated dermoscopic and Wood lamp findings for the diagnosis and classification of all facial melanoses [5]; some studies have only focused on melasma [6-8]. We therefore aimed to evaluate the dermoscopic findings of common facial melanoses and correlate them with findings from Wood lamp examination.

Methods

This was a cross-sectional study conducted at the Department of Dermatology and Venereology, Nepal Medical College and Teaching Hospital (NMCTH), Kathmandu, Nepal. The study subjects included all patients with a facial melanosis who visited the dermatology outpatient department from July 1, 2020, to March 31, 2021. All participants provided written informed consent for participation. The Institutional Review Committee of NMCTH granted approval to conduct the study (reference number 040-076/076).

At the time of enrolment, the investigator filled a form to obtain information on patient age, sex, diagnosis, and Fitzpatrick skin type. The diagnosis was based on clinical examination performed by a dermatologist. Clinical photographs were obtained using iPhone 6s plus (Apple® Inc). A dermatologist examined the participants with a Wood lamp (Dermia India) to assess the depth of pigmentation, and the investigator performed dermoscopic examination (DermLite DL4, 3GenInc).

The data were uploaded onto a secure password-protected database using Microsoft Excel. Data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc). Descriptive statistics were utilized to compute the mean and standard deviation (SD) of age and frequency of facial melanoses. Wood lamp and dermoscopic findings were analyzed using Cohen’s kappa coefficient, and correlation was established. A P value < 0.05 was considered statistically significant.

Results

A total of 204 patients provided informed consent to participate in the study. Most participants were female (146, 71.6%). The mean (SD) age of the participants was 34.04 ± 13.17 years with a range 13-86 years. The highest percentage of participants (72.5%) belonged to the age group 21-40 years. In our sample, 24% had Fitzpatrick skin type III, 65.7% had skin type IV, and 10.3% had skin type V.

The most common diagnosis was melasma (47 patients, 23%) followed by melasma with steroid-induced rosacea-like dermatitis (29 patients, 14.2%). The rarest observed conditions were ashy dermatosis (1 patient), lentigo simplex (1 patient), nevus of Ota (1 patient), and nevus spilus (1 patient). Female predominance was observed in melasma and melasma with steroid-induced rosacea-like dermatitis (13.5:1), and ephelides (100:0). The two patients with nevus of Ota and nevus spilus were males (Table 1).

Wood lamp examination was performed in all patients. Accentuation of pigmentation was observed in all cases of acne-induced postinflammatory hyperpigmentation, blue nevus, café-au-lait macule, compound nevus, dermatoxis papulosa nigra, discoid lupus erythematosus, ephelides, Hori nevus, junctional nevus, lentigo simplex, nevus of Ota, nevus spilus, postinflammatory hyperpigmentation, seborrheic keratosis, solar lentigo and verrucous epidermal nevus. Such accentuation was not observed in patients with ashy dermatosis and peribuccal pigmentation of Brocq. Epidermal as well as dermal pigmentation were observed in melasma, melasma with steroid-induced rosacea-like dermatitis, dermal nevus, periorbital hyperpigmentation and clofazimine induced pigmentation.

The dermoscopic findings of common facial melanoses are given in Table 2. Acne-induced postinflammatory hyperpigmentation was characterized by reddish brown homogenous pigmentation on a reddish background (Figure 1A), and postinflammatory hyperpigmentation secondary to trauma revealed a dark brown reticular or homogenous pattern with dark brown dots (Figure 1B). Dermoscopy of ashy dermatosis and nevus of Ota revealed blue-gray pigmentation forming a curvilinear pattern (Figure 2). Dark brown reticular pattern with follicular sparing was observed in both café-au-lait macule
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Males, n (%)</th>
<th>Females, n (%)</th>
<th>Number, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melasma</td>
<td>9 (19.2)</td>
<td>38 (80.9)</td>
<td>47 (23)</td>
</tr>
<tr>
<td>Melasma with steroid-induced rosacea-like dermatitis</td>
<td>2 (6.9)</td>
<td>27 (93.1)</td>
<td>29 (14.2)</td>
</tr>
<tr>
<td>Compound nevus</td>
<td>10 (37)</td>
<td>17 (63)</td>
<td>27 (13.2)</td>
</tr>
<tr>
<td>Ephelides</td>
<td>0</td>
<td>16 (100)</td>
<td>16 (7.8)</td>
</tr>
<tr>
<td>Acne-induced postinflammatory hyperpigmentation</td>
<td>6 (46.2)</td>
<td>7 (53.8)</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>Blue nevus</td>
<td>5 (41.7)</td>
<td>7 (58.3)</td>
<td>12 (5.9)</td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td>6 (54.5)</td>
<td>5 (45.5)</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>Junctional nevus</td>
<td>4 (44.4)</td>
<td>5 (55.6)</td>
<td>9 (4.4)</td>
</tr>
<tr>
<td>Periorbital hyperpigmentation</td>
<td>4 (57.1)</td>
<td>3 (42.9)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Solar lentigo</td>
<td>2 (40)</td>
<td>3 (60)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Dermatosis papulosa nigra</td>
<td></td>
<td>4 (100)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Postinflammatory hyperpigmentation</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Clofazimine-induced pigmentation</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
<td>2 (66.7)</td>
<td>1 (33.3%)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Café-au-lait macule</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dermal nevus</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hori nevus</td>
<td>0</td>
<td>2 (100)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Peribuccal pigmentation of Brocq</td>
<td>0</td>
<td>2 (100)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Verrucous epidermal nevus</td>
<td>0</td>
<td>2 (100)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Ashy dermatosis</td>
<td>0</td>
<td>1 (100)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Lentigo simplex</td>
<td>0</td>
<td>1 (100)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Nevus of Ota</td>
<td>1 (100)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Nevus spilus</td>
<td>1 (100)</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (28.4)</td>
<td>146 (71.6)</td>
<td>204</td>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Dermoscopic Features</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne-induced postinflammatory hyperpigmentation</td>
<td>Brown structureless areas</td>
<td>78.6%</td>
</tr>
<tr>
<td></td>
<td>Brown reticular pattern</td>
<td>64.3%</td>
</tr>
<tr>
<td>Ashy dermatosis</td>
<td>Blue gray pigmentation forming a curvilinear pattern</td>
<td>100%</td>
</tr>
<tr>
<td>Blue nevus</td>
<td>Blue gray homogenous pattern</td>
<td>100%</td>
</tr>
<tr>
<td>Café-au-lait macule</td>
<td>Light brown reticular pattern</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Blue gray dots</td>
<td>50%</td>
</tr>
<tr>
<td>Clofazimine induced pigmentation</td>
<td>Coppery red background</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Brown homogenous pattern</td>
<td>66.7%</td>
</tr>
<tr>
<td></td>
<td>Hem-like pattern</td>
<td>66.7%</td>
</tr>
<tr>
<td>Compound nevus</td>
<td>Diffuse black homogenous pattern</td>
<td>51.9%</td>
</tr>
<tr>
<td></td>
<td>Dark brown globular pattern</td>
<td>18.5%</td>
</tr>
<tr>
<td>Dermal nevus</td>
<td>Cobblestone pattern, Tan structureless area</td>
<td>100%</td>
</tr>
<tr>
<td>Dermatosis papulosa nigra</td>
<td>Fissures and ridges, milia-like cysts, moth-eaten border</td>
<td>100%</td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
<td>Follicular keratotic plugs, dark brown pigmentation</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Perifollicular halo, White structureless areas</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Telangiectatic vessels</td>
<td>100%</td>
</tr>
<tr>
<td>Ephelides</td>
<td>Brown reticular pattern with moth-eaten border</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Dark brown dots</td>
<td>93.8%</td>
</tr>
<tr>
<td>Hori nevus</td>
<td>Bluish brown blotch</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2 continues
Table 2. Dermoscopic Features of Facial Melanoses. (continued)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Dermoscopic Features</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junctional nevus</td>
<td>Dark brown reticular pattern</td>
<td>55.6%</td>
</tr>
<tr>
<td></td>
<td>Light brown reticular pattern, Interspersed brown dots</td>
<td>33.3%</td>
</tr>
<tr>
<td>Lentigo simplex</td>
<td>Brown reticular pattern with moth-eaten border</td>
<td>100%</td>
</tr>
<tr>
<td>Melasma</td>
<td>Arciform structures</td>
<td>85.1%</td>
</tr>
<tr>
<td></td>
<td>Telangiectasia</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Dark brown to bluish gray reticular pattern</td>
<td>61.7%</td>
</tr>
<tr>
<td></td>
<td>Light brown reticular pattern</td>
<td>44.3%</td>
</tr>
<tr>
<td>Melasma with steroid-induced rosacea-like dermatitis</td>
<td>Telangiectasias</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Arciform structures</td>
<td>93.1%</td>
</tr>
<tr>
<td></td>
<td>Dark brown to bluish gray reticular pattern</td>
<td>79.3%</td>
</tr>
<tr>
<td></td>
<td>Light brown reticular pattern</td>
<td>55.2%</td>
</tr>
<tr>
<td></td>
<td>Dilated tortuous branched vessels giving a polygonal appearance</td>
<td>48.3%</td>
</tr>
<tr>
<td></td>
<td>Terminal hair</td>
<td>17.2%</td>
</tr>
<tr>
<td>Nevus of Ota</td>
<td>Blue gray pigmentation forming a curvilinear pattern</td>
<td>100%</td>
</tr>
<tr>
<td>Nevus spilus</td>
<td>Light brown reticular pattern</td>
<td>100%</td>
</tr>
<tr>
<td>Peribuccal pigmentation of Brocq</td>
<td>Dark brown reticular pattern</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Dark brown hem-like pattern</td>
<td>50%</td>
</tr>
<tr>
<td>Periorbital hyperpigmentation</td>
<td>Dark brown reticular pattern</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Dark brown hem-like pattern</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Cobblestone pattern</td>
<td>57.1%</td>
</tr>
<tr>
<td>Postinflammatory hyperpigmentation</td>
<td>Dark brown reticular pattern</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Moth-eaten borders</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Dark brown homogenous pattern</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Dark brown peripheral reticular pattern with central hypopigmentation</td>
<td>25%</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>Milia-like cysts</td>
<td>63.6%</td>
</tr>
<tr>
<td></td>
<td>Fissures and ridges</td>
<td>54.5%</td>
</tr>
<tr>
<td></td>
<td>Comedo-like openings</td>
<td>36.4%</td>
</tr>
<tr>
<td></td>
<td>Fingerprint-like structures</td>
<td>27.3%</td>
</tr>
<tr>
<td>Solar lentigo</td>
<td>Brown reticular pattern, Fingerprint-like structures</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Moth-eaten border</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Brown structureless homogenous pigmentation</td>
<td>80%</td>
</tr>
<tr>
<td>Verrucous epidermal nevus</td>
<td>Large brown circles with hyperchromic brown edge surrounding a hypochromic areata</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Exophytic structures</td>
<td>50%</td>
</tr>
</tbody>
</table>

Figure 1. Dermoscopic image. (A) acne-induced post inflammatory hyperpigmentation showing homogenous dark brown pattern on a reddish background. (B) trauma-induced postinflammatory hyperpigmentation showing reticular dark brown pattern with dark brown dots.
Figure 2. Dermoscopic image revealing blue gray pigmentation forming a curvilinear pattern (square). (A) ashy dermatosis. (B) nevus of Ota.

Figure 3. Dermoscopic image. (A) café-au-lait macule displaying a dark brown reticular pattern (rectangle) with dark brown dots (circle). (B) nevus spilus showing a reticular pattern (rectangle) with follicular sparing and perifollicular accentuation (circle).

and nevus spilus. In addition to the reticular pattern, the café-au-lait macule displayed dark brown dots and perifollicular accentuation was observed in nevus spilus (Figure 3).

Clofazimine-induced pigmentation, peribuccal pigmentation of Brocq, and periorbital pigmentation revealed a reticular and hem-like pattern of pigmentation on dermoscopy (Figure 4). The background was coppery red in clofazimine-induced pigmentation but not in the other two conditions (Figure 4). Hori nevus showed a speckled bluish brown pattern of pigmentation (Figure 5), and verrucous epidermal nevus revealed large brown circles with a hyperchromic brown edge surrounding a hypochromic area.

Melasma and melasma with steroid-induced rosacea-like dermatitis were classified into epidermal, dermal, and mixed types based on dermoscopic findings. The epidermal type was characterized by the presence of scattered islands of a light brown reticular network and the dermal type by dark brown to bluish gray irregular pigment network and arciform structures. The mixed type had presence of epidermal and dermal features (Figure 6). There were 8 (17.0%) epidermal,
Figure 4. Dermoscopic picture showing dark brown hem-like pigment pattern (rectangle). (A) clofazimine-induced pigmentation on a coppery background. (B) peribuccal pigmentation of Brocq. (C) periorbital hyperpigmentation.

Figure 5. Dermoscopic image. (A) Hori nevus showing speckled bluish brown pigmentation. (B) verrucous epidermal nevus showing large brown circles with hyperchromic brown edge surrounding a hypochromic area (rectangle).
Figure 6. Clinical, Wood lamp examination, and dermoscopic images in epidermal, dermal, and mixed melasma. (A) Epidermal melasma showing faint hyperpigmented macules in bilateral malar region showing accentuation. (B) on Wood lamp examination. (C) Light brown reticular pattern (rectangle) and brown dots (circle) on dermoscopy. (D) Dermal melasma with dark brown hyperpigmented macules on the forehead. (E) Malar region showing masking of pigmentation on Wood lamp examination. (F) Dark brown irregular pigment network (rectangle), arciform structures (circle) and telangiectasia (pentagon) on dermoscopy. (G) Mixed melasma displaying light brown hyperpigmented macules on periorbital and forehead regions displaying accentuation on forehead. (H) Masking on malar region on Wood lamp examination. (I) Dermoscopy shows light brown (rectangle) and dark brown (hexagon) pigment networks, arciform structures (diamond), and telangiectasia (pentagon).

Table 3. Correlation Between Wood lamp and Dermoscopic Findings in Melasma and Melasma with Steroid-Induced Rosacea-Like Dermatitis

<table>
<thead>
<tr>
<th>Melasma</th>
<th>Dermoscopy</th>
<th>χ²-value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood’s lamp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal</td>
<td></td>
<td>60.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Dermal</td>
<td></td>
<td>27.7%</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>36.2%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>38.3%</td>
<td></td>
</tr>
</tbody>
</table>

Kappa statistics = 0.701, P = 0.0001 (significant)
Table 3. Correlation Between Wood lamp and Dermoscopic Findings in Melasma and Melasma with Steroid-Induced Rosacea-Like Dermatitis (continued)

<table>
<thead>
<tr>
<th></th>
<th>Melasma With Steroid-Induced Rosacea-Like Dermatitis</th>
<th>Dermoscopy</th>
<th>$\chi^2$ value</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood’s lamp</td>
<td>Epidermal</td>
<td>Dermal</td>
<td>Mixed</td>
<td>Total</td>
</tr>
<tr>
<td>Epidermal</td>
<td>6 (20.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Dermal</td>
<td>0 (0%)</td>
<td>8 (27.6%)</td>
<td>2 (6.9%)</td>
<td>10 (34.5%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>0 (0%)</td>
<td>5 (17.2%)</td>
<td>8 (27.6%)</td>
<td>13 (44.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>6 (20.7%)</td>
<td>13 (44.8%)</td>
<td>10 (34.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Kappa statistics = 0.628, $P = 0.0001$ (significant)

Figure 7. Clinical, Wood lamp examination and dermoscopic images in epidermal, dermal, and mixed melasma with steroid-induced rosacea-like dermatitis. (A) Epidermal melasma with steroid-induced rosacea-like dermatitis showing faint hyperpigmented macules in bilateral malar region. (B) accentuation on Wood lamp examination. (C) light brown reticular pattern (rectangle), dilated tortuous vessels (oval) forming a polygonal pattern (diamond) on dermoscopy. (D) Dermal melasma with steroid-induced rosacea-like dermatitis with dark brown hyperpigmented macules on forehead and malar region and erythema on bridge of nose. (E) masking of pigmentation on Wood lamp examination. (F) dark brown homogenous pigmentation (rectangle), dilated tortuous vessels (telangiectasia) forming a polygonal pattern (oval) on dermoscopy. (G) Mixed melasma displaying light brown hyperpigmented macules on malar region with faint erythema displaying accentuation on malar. (H) masking on the forehead region on Wood lamp examination. (I) Dermoscopy shows light brown (hexagon) and dark brown (rectangle) pigment network with red structureless areas (oval).
21 (44.7%) dermal and 18 (38.3%) mixed types of melasma. A similar pattern was observed in melasma with steroid-induced rosacea-like dermatitis: epidermal (6, 20.7%), dermal (13, 44.8%), mixed (10, 34.5%).

The degree of agreement between Wood lamp and dermoscopic findings was found to be substantial as analyzed by kappa statistics (Table 3). Of the 8 lesions considered as epidermal type by dermoscopy, the examination agreement under Wood lamp was 100%. Of the 21 considered dermal by dermoscopy, the agreement with Wood lamp was only 44.8%. And of the 18 considered mixed by dermoscopy, the agreement was 94.4% with Wood lamp examination.

Regarding melasma with steroid-induced rosacea-like dermatitis, 6 cases were classified as epidermal, 13 as dermal and 10 as mixed type. The agreement with Wood lamp examination was 100% for epidermal, 61.5% for dermal and 80.0% for mixed type. In addition, dermoscopy revealed follicular sparing with perifollicular accentuation (96.6%), arcuate structures (93.1%), dilated tortuous branched vessels giving a polygonal appearance (44.8%) and terminal hairs (10.3%) (Figure 7).

Although the two cases of dermal nevus showed different patterns of autofluorescence on Wood lamp examination, there were no differences detected in dermoscopic examination. The three cases of dermal periorbital hyperpigmentation revealed dark brown reticular and hem-like pattern on dermoscopy while the epidermal cases showed cobblestone pattern in addition to the above features. Dark brown blotches, hem-like pattern on a coppery red background were observed in epidermal clofazimine-induced pigmentation while blotches were not seen in dermal clofazimine-induced pigmentation.

Conclusions

In our study, melasma was the most frequent diagnosis followed by melasma with steroid-induced rosacea-like dermatitis. Epidermal melasma was characterized by light brown reticular network, dermal by dark brown to bluish gray irregular pigment network and arciform structures and mixed by features of both epidermal and dermal types. Nanjundaswamy et al [9] also observed scattered islands of brown reticular network in epidermal melasma. Dermal melasma showed uniform skin involvement with dark brown to gray hyperpigmented irregular pigment network. Yalamanchili et al [10] also found light or dark brown, diffuse or patchy reticular pigmentation in 95% of patients with melasma.

Few studies have compared Wood lamp and dermoscopic findings in melasma. Talamer et al [6], in their study done in Brazil, found 44% agreement in epidermal melasma, 57% in dermal melasma and 51% in mixed melasma. The degree of concordance was considered weak (k < 0.2). Two studies done in India found a substantial degree of agreement between Wood’s lamp and dermoscopic findings in melasma. Dharni et al [7] found correlation between the two techniques in 56.25% of patients and the degree of agreement was statistically significant (k = 0.813, P = 0.0001). Manjunath et al [8] also found a good degree of correlation (k = 0.833, P = 0.0001). In our study too, the degree of agreement was significant (k = 0.701, P = 0.000). However, while the degree of agreement was 100% for epidermal type, it was only 44.8% for dermal melasma. The discrepancies could be attributed to better visualization of arciform structures and dark brown to bluish gray irregular pigment network in dermal melasma with dermoscopy.

In our setting, melasma with steroid-induced rosacea-like dermatitis is frequently encountered [3]. The main dermoscopic features identified were light to dark brown reticular pigment network, arcuate structures, dilated tortuous branched vessels giving a polygonal and terminal hairs. Jakhar et al [11] in their case report on topical steroid dependent/damaged face discovered dilated tortuous branched vessels interconnecting with each other to form a polygonal pattern on dermoscopy. In addition, white structureless areas, yellowish areas and coarse terminal hairs were also visible [11]. According to them, white structureless areas correspond to dermal atrophy. We did not encounter white structureless areas in our study indicating that this could be an incidental finding. We also found correlation between Wood lamp and dermoscopic classification of melasma with steroid-induced rosacea-like dermatitis (k = 0.628, P = 0.0001), which has not yet been reported in the literature. Here again, while agreement was 100% in epidermal type, it decreased to 61.5% for dermal and 80% for mixed type. Thus, while Wood lamp examination may help to differentiate epidermal melasma from other types of conditions, it may not be so accurate for dermal or mixed melasma with steroid-induced rosacea-like dermatitis.

In this study, we had one patient with ashy dermatosis and one with nevus of Ota. The dermoscopic findings in both the cases were similar; blue gray pigmentation forming a curvilinear pattern. Gray dots and globules having an irregular linear arrangement in ashy dermatosis has also been reported by Elmas et al [12]. This arrangement has been named as broken lines and semi-arcuate structures appearing as Chinese letters by Vinay et al [13]. Blue gray pigmentation forming a curvilinear pattern on dermoscopic examination of nevus of Ota has not yet been described in the literature. In the study done by Elmas et al [14], the most common dermoscopic findings of nevus of Ota were brown and gray structureless areas having a patchy distribution. They also observed white clods in a “four dots clod” arrangement. El-Kadi et al [15] observed blue grayish structureless areas with iridescent reflections and white rosettes in their case report on nevus of Ota. A
curvilinear pattern could be discerned in the dermoscopic image in their case report, although it was not mentioned by the authors. Whether a curvilinear pattern is a characteristic feature of nevus of Ota remains to be explored.

Dark brown blotches, hem-like pattern of pigmentation on a coppery red background were observed on dermoscopic examination of patients with clofazimine-induced pigmentation. We identified only one study that had evaluated dermoscopic findings in clofazimine-induced pigmentation. Chopra et al [16] described honeycomb pattern with yellow to white globules interspersed along a dark to skin-colored background. To best of our knowledge, this is the first study identifying hem-like pattern of pigmentation in clofazimine-induced pigmentation.

We had seven cases of periorbital hyperpigmentation out of which four displayed accentuation of pigmentation on Wood lamp examination. All cases showed dark brown reticular and hem-like pigmentation on dermoscopic examination. The epidermal cases showed a cobblestone pattern in addition to the above features. Jage et al [17] evaluated the dermoscopic findings in 50 patients with periorbital hyperpigmentation in 2018. The most common findings were blotches, exaggerated pigment network, coarse speckled, fine speckled and globules. Skin changes included atrophy and exaggerated skin markings. We believe the hem-like pigmentation (increased pigmentation along the skin folds) seen on dermoscopy corresponds to exaggerated skin markings. The exaggerated skin markings imply an atopic diathesis, post-steroid abuse or constitutional type of periorbital hyperpigmentation [17].

There were some notable limitations in the study. As it was a cross-sectional study, we could not obtain longitudinal data. This was especially true for discoid lupus erythematosus and ephelides, which have waxing and waning courses. Our hospital-based study also may be not?? representative of the general population.

Another limitation of our study is the relatively small sample size and the lack of histopathological correlation with dermoscopic examination. As this study took place during the peak of the COVID-19 epidemic in Nepal, this affected the sample size. Furthermore, most patients chose not to undergo an invasive procedure like biopsy for histopathological confirmation. We recommend future studies exploring correlation between dermoscopic and histopathological findings in all facial melanoses as dermoscopic information provided to pathologist can improve diagnostic accuracy.

The most frequent diagnoses in our study were melasma, melasma with steroid-induced rosacea-like dermatitis and various types of naevi. Dermoscopy of ash hyperpigmentation and naevi of Ota revealed blue gray pigmentation forming a curvilinear pattern. Café-au-lait macule and nevus spilus revealed light brown reticular pattern with follicular sparing on dermoscopy. Reticular and hem-like pattern of pigmentation was observed on dermoscopy of clofazimine-induced pigmentation, peribuccal pigmentation of Brocq and periorbital pigmentation. Although the degree of agreement between Wood lamp and dermoscopic findings were found to be statistically significant in the different types of melasma and melasma with steroid-induced rosacea-like dermatitis, the agreement was higher for epidermal types and less for dermal and mixed types. We recommend further studies exploring dermoscopic, Wood lamp and histological findings in all facial melanoses.

References


Comparison of Actinic Keratosis and Severity Index with Physician Global Assessment and Total Lesion Count and the Ability to Predict Skin Cancer

Ayda Acar¹, Isil Karaarslan¹

¹Ege University, Medical Faculty, Department of Dermatology and Venereology, Izmir, Turkey

Key words: actinic keratosis, AKASI, physician global assessment, skin cancer, total lesion count

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Corresponding author: Ayda Acar, MD, Department of Dermatology, Ege University Faculty of Medicine, University Street Bornova, Izmir, Turkey. E-mail: aydaerbas@yahoo.com

ABSTRACT

Introduction: Actinic keratosis (AK) is a known indicator for sun damage, and subsequent squamous cell cancer may develop. The actinic keratosis and severity index (AKASI) is a recently developed tool that can evaluate both field cancerization and AK severity.

Objectives: We sought to evaluate if AKASI was a good predictor of cancer in AK patients and to compare AKASI with both the Physician Global Assessment (PGA) and total lesion count (TLC).

Methods: Ninety patients with AK were included in the study. Each patient was examined, and AKs were scored with AKASI, PGA and TLC by 2 dermatologists. The AKASI, PGA and TLC values were compared between patients with skin cancer and patients without skin cancer.

Results: Mean AKASI, PGA, and TLC scores were 4.9, 1.7 and 9 respectively. The patients with skin cancer had higher scores of AKASI, PGA and TLC compared to the patients without skin cancer (P = 0.022, P = 0.014, P = 0.005, respectively). AKASI, PGA and TLC were very strongly correlated with each other (P < 0.001). The AKASI threshold value for non-melanoma skin cancer was determined to be 5.1.

Conclusions: AKASI, PGA and TLC may be used in the assessment of the severity of AK in daily practice or studies and may be considered as valuable tools in determining high-risk patients and to choose treatment option. AKASI seems to have an advantage to give a numeric threshold value for skin cancer.
Introduction

Actinic keratoses (AK) are hyperkeratotic lesions on sun-damaged skin characterized by atypical epidermal proliferation of keratinocytes that have a potential for malignant transformation to squamous cell carcinoma (SCC). They are generally asymptomatic, erythematous, or pigmented papules or plaques with scales, located on sun-exposed areas like the face, scalp, ear helices, and dorsum of the hand [1]. Excessive exposure to ultraviolet (UV) radiation is the major cause of AK. Fairer skin types, older age, chronic use of systemic immunosuppressive drugs, and exposure to arsenic have also been described as risk factors [2-4]. In addition to immunosuppressive drugs, other drugs, such as voriconazole, calcium channel blockers, BRAF inhibitors, hedgehog inhibitors, hydroxyurea, and psoralen plus UVA therapy have been linked to a higher risk for AK and SCCs [5-8]. On the other hand, oral retinoids and nicotinamide have been linked to a reduction in the risk of AK and SCC [9].

The estimated risk for an individual AK to transform into SCC has been reported to be 0.075%-0.096% annually [2]. Although most of AKs regress spontaneously or persist without a malignant transformation, the major concern is the difficulty in estimating which lesion might have a higher potential for malignancy. The thickness or hyperkeratosis of an individual AK lesion does not have equal SCC progression risk [10]; thus, treatment is highly recommended for each AK lesion. In recent years, the term field cancerization (FC), which describes an area of severe sun damage with multiple AKs, telangiectasia, wrinkles, dyschromia and elastosis, has been proposed [11] and FC treatment has been recommended for a better management of the patients [3]. The identification of patients with a higher risk for malignant transformation is another important issue to consider when deciding which patients should be included in a closer follow-up program.

There have been some efforts to grade the risk of patients with malignant potential. The Physician Global Assessment (PGA) scale is a subjective assessment tool that allows the physician to evaluate the overall situation of the patient [12]. PGA grades AKs in five categories (0: clear, 1: almost clear, 2: mild, 3: moderate, 4: severe) [12]. The total lesion count (TLC), in which physician counts the clinically evident AK lesions, is another suggested way to evaluate a patient both before and after the therapy [13]. Recently, the actinic keratosis and severity index (AKASI) has been suggested [12]. The AKASI supplies a numerical score on an index and evaluates both the severity of AK and FC (Table 1) [12]. AKASI has also been reported to be useful in monitoring treatment outcomes [10]. In AKASI score, the head is divided into 4 regions: scalp, forehead, left face (cheek, ear, chin, and nose), and right face. The scalp constitutes 40% of the head region, and each of the other areas constitutes 20%. For each of the 4 areas, the percentage of actinic damage is scored 0 to 6. The most prominent AK distribution, erythema, and thickness are assessed from 0-4. The maximum AKASI value is 18. The pivotal study proposed an AKASI score of 2.9 as mild, 5.3 as moderate, 8.3 as severe, 8.7 as very severe [12].

Objectives

In the literature, the data on the association between non-melanoma skin cancer and AKASI, PGA, and TLC is limited [14]. In this study, we sought to evaluate this association and discuss the ability of these methods to predict skin malignancy.

Methods

The study was approved by the local ethics committee (no: 70198063-050.06.04). Patients with AK, who were referred to our dermato-oncology unit within a 6-month period and who signed the informed consent form, were involved in the study. Patients with a history of photosensitivity, non-melanoma skin cancer (NMSC)-prone genodermatoses, and melanoma were excluded.

A detailed anamnesis on accompanying diseases, drug usage, previous history of NMSC, duration of the present lesions, and the Fitzpatrick skin type were recorded. A total-body skin and dermoscopic examination were performed for each patient. The patients were examined by 2 dermatologists at the same time in order to avoid any interobserver variability. The AKASI, PGA and TLC values were noted.

Descriptive statistics of the data were given as mean, standard deviation, median, minimum, maximum, frequency and percentage values. Normality assumption of quantitative data was checked by Shapiro-Wilk test. Independent sample t-test was used for variables with normal distribution, while Mann-Whitney U test and Kruskal-Wallis test (Dunn test for paired comparisons) were used for variables that did not provide the assumption of normality. The correlation of quantitative data with each other was evaluated with Spearman Rho correlation coefficient. Relationships between categorical variables were examined using the Pearson Chi-square test. A receiver operating characteristic (ROC) analysis was used to determine a cutoff point for diagnostic methods. Statistical analysis was performed using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, Version 25.0, IBM) package program. The significance level was set at 0.05 in all analyses.
Table 1. Definition of Components of Actinic Keratosis Area and Severity Index (AKASI) and How to Calculate AKASI Score*

<table>
<thead>
<tr>
<th>AKASI Components</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solar damage (SD)</td>
<td>Head is divided to 4 areas: scalp (S), forehead (F), right half of the face (R), left half of the face (L). Skin with solar damage for each of the 4 areas is estimated and scored 0-6. 0 (0%), 1 (1-9%), 2 (10-29%), 3 (30-49%), 4 (50-69%), 5 (70-89%), 6 (90-100%).</td>
</tr>
<tr>
<td>Distribution of AK (D)</td>
<td>0: No AK. 1: Isolated or scattered AK. 2: Clustered (Small clusters up to 25 cm²). 3: Clustered and confluent (AKs are coalescing in a cluster of &lt;25 cm²). 4: Confluent (AKs are coalescing and cannot be easily distinguish).</td>
</tr>
<tr>
<td>Distribution of AK (D)</td>
<td>0: No AK. 1: Isolated or scattered AK. 2: Clustered (Small clusters up to 25 cm²). 3: Clustered and confluent (AKs are coalescing in a cluster of &lt;25 cm²). 4: Confluent (AKs are coalescing and cannot be easily distinguish).</td>
</tr>
<tr>
<td>Erythema of AK (E)</td>
<td>0: No erythema. 1: Slight red. 2: Moderate red. 3: Intense red. 4: Very intense red.</td>
</tr>
<tr>
<td>Thickness of AK (T)</td>
<td>0: No palpable or visible AK. 1: Just palpable AK. 2: Clearly palpable. 3: Thickened. 4: Very thickened.</td>
</tr>
<tr>
<td>Total AKASI score (0-18)</td>
<td>0.4 x (D+E+T+SD of scalp) + 0.2 x (D+E+T+SD of forehead) + 0.2 x (D+E+T+SD of right face) + 0.2 x (D+E+T+SD of left face)</td>
</tr>
</tbody>
</table>

*Adapted from the report of Dirschka et al [12].

AK = actinic keratosis; AKASI = actinic keratosis area and severity index.

Results

A total of 90 patients were involved in the study. Fifty-four patients (60%) were males. The age range was 48-87 years (mean age was 69 years and median age was 71). The accompanying diseases were hypertension (43%), diabetes mellitus (27%), coronary arterial disease (CAD) (14%), solid organ malignancy (13%), inflammatory or autoimmune skin diseases (13%), solid organ transplantation (6%) and others (asthma, vertigo, Parkinson disease, migraine, gut, essential thrombocytosis, familial Mediterranean fever, hepatitis B) (10%). Fourteen patients (16%) were receiving calcium channel blockers, 9 patients (10%) were receiving immuno-suppressive drugs, and 1 patient was receiving hydroxyurea. The distribution of Fitzpatrick skin type was as follows: 73 patients (81%) had Fitzpatrick skin type II and 17 patients (19%) had type III. The duration of the present AK lesions ranged from 2 months to 30 years. The mean duration was 7 years. Mean AKASI was 4.9, mean PGA was 1.7 and mean TLC was 9.3. Mean AKASI was 6 in male patients and 3 in female patients. The difference between male and female patients was statistically significant (P < 0.001). Mean PGA was 2 in male and 1 in female patients. Mean TLC was 11 in male and 7 in female patients. The difference between male and female patients of PGA and TLC was statistically significant (P < 0.001, P = 0.002).
Fifty-one patients (57%) did not have any current skin cancer or skin cancer history. A total of 39 patients (43%) had a current skin cancer and/or past history of skin cancer. Among them, 28 patients (31.1%) had only previous skin cancer history, 8 patients (8.8%) had only concurrent skin cancer, and 3 patients (3.3%) had both concurrent skin cancer and previous skin cancer history. Nineteen patients (21.1%) had only basal cell carcinoma (BCC) and BCC count was 26. Thirteen patients (14.4%) had only SCC and SCC count was 21. Seven patients (7.7%) had both SCC and BCC, tumor count was 29 (11 for SCC and 18 for BCC). One patient who had both BCC and SCC also had 2 basosquamous cell carcinomas. Total tumor count was 78 (44 for BCC, 32 for SCC, and 2 for basosquamous cell carcinoma). In all but 7 patients all the tumors were located on the face or scalp. In 7 patients, 14 tumors (8 BCCs and 6 SCCs) were located on an extremity or trunk. None of the patients had skin cancer metastasis.

All items were compared between the group with previous or present skin cancer (Group A, n = 39) and the group with no history of skin cancer (Group B, n = 51) (Table 2). The mean age in group A was 70 years (median 73 years), and the mean age in group B was 69 years (median 70 years). The mean age of the patients was higher in the group with skin cancer, but it was not statistically significant (P = 0.261). Mean and median AK duration was longer in the group A (mean 9, median 9) compared to the group B (mean 6, median 5). Having longer AK duration in the group A was statistically significant (P = 0.009). The distribution of demographic features and scores of AKASI, PGA and TLC in the two groups are shown in Table 2. There was no statistically significant relationship between having skin cancer and gender (P = 0.794), or accompanying diseases. However statistically significant relationship was found with not having CAD (P = 0.028). AK duration was significantly related with AKASI, PGA and TLC scores (P = 0.038, P = 0.010, P = 0.016). Mean and median AKASI, PGA score and TLC were higher in group A (mean 6, median 6; mean 2, median 2; and mean 11, and median 11, respectively) compared to group B (mean 4, median 4; mean 2, median 1 and mean: 8, and median 7, respectively) (Table 2). The higher scores of AKASI, PGA and TLC in group A were statistically significant (P = 0.022, P = 0.014, P = 0.005).

Nineteen patients with high risk drugs or diseases for skin cancer had higher AKASI scores and it was statistically significant (P = 0.033). These patients had also higher mean PGA and TLC values, which were not statistically significant (P = 0.077, P = 0.221).

Patients were also grouped as no skin cancer (group I, n = 51 patients), patients with only BCC (group II, n = 19 patients), patients with only SCC (group III, n = 13 patients), and patients with both BCC and SCC (group IV, n = 7 patients). Mean AKASI score, PGA, and TLC were highest in group IV. The ranking of mean values of scores was: group III, II, and I respectively. The increase in the mean values of AKASI, PGA, and TLC from group I to group IV was statistically significant (P = 0.026, P = 0.026, P = 0.038). The total number of skin cancer counts (previous and present) were not related with AKASI, PGA, and TLC (P = 0.064, P = 0.075, P = 0.149).

AKASI, PGA, and TLC were correlated with each other (P < 0.001). Correlation between AKASI and PGA, between AKASI and TLC, and between PGA and TLC were very strong (r = 0.881, r = 0.893, r = 0.849). As a result of ROC analysis, the AKASI threshold value for total NMSC was determined to be 5.1 (P = 0.022, area = 0.642). The AKASI thresholds for SCC and BCC according to ROC analysis were 5.5 (P = 0.036, area = 0.682) and 6.9 (P = 0.926, area = 0.509), respectively. Total NMSC threshold value was statistically significant. However, threshold values for only BCC or only SCC groups were not statistically significant.

### Table 2. Comparison Between the Group with Previous or Present Skin Cancer (Group A) and the Group with No History of Skin Cancer (Group B).

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male percent</td>
<td>62%</td>
<td>59%</td>
</tr>
<tr>
<td>Mean and median age</td>
<td>70, 73</td>
<td>69, 70</td>
</tr>
<tr>
<td>Mean and median AK duration (years)</td>
<td>9, 9</td>
<td>6, 5</td>
</tr>
<tr>
<td>Mean and median AKASI</td>
<td>6, 6</td>
<td>4, 4</td>
</tr>
<tr>
<td>Mean and median PGA</td>
<td>2, 2</td>
<td>2, 1</td>
</tr>
<tr>
<td>Mean and median TLC</td>
<td>11, 11</td>
<td>8, 7</td>
</tr>
</tbody>
</table>

AK = actinic keratosis; AKASI = actinic keratosis area and severity index; PGA = Physician Global Assessment; TLC = total lesion count.
Conclusions

In order to determine the malignant transformation risk in AK, there is a need for scoring the disease extent and overall severity rather than evaluating the individual lesion. PGA and TLC have been used for determining the severity of AK. Recently, in 2017, AKASI was proposed by Dréno et al [12]. In 2018, Pellacani et al compared AKASI with TLC [13] and found AKASI a reproducible method that can be used in clinical trials as an alternative to TLC. Although no significant difference was found between AKASI and TLC in the interobserver variability, AKASI had a slightly higher intra-class correlation coefficient compared to TLC. They stated that either of the 2 methods could be used [13]. In 2018, Schmitz et al investigated the association between AKASI and keratinocytic tumors [14]. They concluded patients with SCC had a higher AKASI score compared to patients with BCC, Bowen disease or AK solely [14]. Schmitz et al suggested that the AKASI score of 3 is consistent with mild, 5.5 moderate, 8.5 severe, and > 11 very severe AK. Their estimated AKASI score for invasive SCC development was found to be 7, median AKASI scores of 4.8, and 7.1 and PGA 2 and 2.5 in patients with BCC and SCC respectively [14]. Additionally, AKASI was used in studies evaluating AK treatment outcomes [10, 15-18].

In 2017, Dréno et al [19] recommended the actinic keratosis field assessment scale (AK-FAS) to evaluate the severity of AK and sun damage, as AK-FAS evaluates AK area percentage, hyperkeratosis and sun damage. The AK area is graded as I-IV (< 10%, 10%-25%, > 25%-50%, and > 50%) according to percentage of AK covering the face or scalp. Hyperkeratosis and sun damage are assessed as absent or present [19]. In 2019, AKFAS together with AKASI was used in a study of both dermoscopic and reflectance confocal microscopic evaluation of AK before and after imiquimod therapy [15]. We preferred to use AKASI over AK-FAS because AK-FAS does not provide a numerical value as AKASI does.

In the present study, the median AKASI, PGA, and TLC values were found to be significantly higher in patients with NMSC compared with patients without NMSC. These values were highest in the patients who had both BCC and SCC and in the patients who had SCC alone. Additionally, AKASI, PGA, and TLC were well correlated. The AKASI threshold value for NMSC was determined to be 5.1; male patients had significantly higher AKASI, PGA, and TLC scores compared to female patients. The patients with current skin cancer or skin cancer history had significantly longer AK duration, higher AKASI, PGA, and TLC scores compared to patients without skin cancer or history of skin cancer. Patients who had an immunosuppressive condition (drugs, solid organ transplantation, and systemic malignancy) had significantly higher AKASI scores compared to patients without an immunosuppressive condition.

Our study employed AKASI, PGA and TLC to assess the severity of AK and to evaluate the relationship with malignancy risk. We conclude that AKASI, PGA, and TLC may be used in the assessment of the severity of AK in daily practice or studies. Although a longer period is needed for calculation of AKASI, it seems advantageous to have a numerical threshold value for skin cancer. This is the second study that evaluates this threshold value in the literature. To establish a common value, more studies are needed.

References


Study of the Visceral Adipose Tissue in a Cohort of Patients with Moderate-Severe Psoriasis Treated with Biological Therapy

Ruiz-Villaverde Ricardo, Ruiz-Carrascosa José C

1 Dermatology Department, Hospital Universitario San Cecilio, Granada, Spain

Key words: psoriasis, biological therapy, visceral adipose tissue, treatment, severity.

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Corresponding author: Ricardo Ruiz-Villaverde. Servicio de Dermatología. Hospital Universitario San Cecilio, Granada, Spain. E-mail: ismenios2005@gmail.com

ABSTRACT

Introduction: Visceral adipose tissue (VAT) has a greater relationship with the genesis of the metabolic syndrome and the pathology associated with obesity.

Methods: A cross-sectional study of patients with moderate-severe psoriasis in the Psoriasis Unit of the San Cecilio University Hospital in Granada in the period July 1, 2020 - December 31, 2020, was performed. All the patients (n = 110) were receiving biological therapy to control the disease. The variables measured included age, sex, time since diagnosis, weight, height, body mass index (BMI), visceral and total fat, and severity parameters. The visceral fat index was evaluated using a bioimpedance scale, considering a cut-off point for a healthy level < 12.

Results: Our sample consisted of 110 patients with a mean age of 47.47 years, with a clear predominance of males (61.7% of patients). After testing for normality using the Kolmogorov-Smirnov test, the Mann-Whitney U test for nonparametric data for independent samples was used, which revealed significant differences between the number of previous treatments and visceral fat (U = -2.235, P = 0.025). No statistically significant differences were found when correlating total fat or visceral fat with BMI.

Conclusions: The results presented lead us to consider if the levels of VAT could be a factor that contributes to some extent to therapeutic refractoriness. The determination of VAT using bioimpedance scales in patients with moderate-severe psoriasis is a valuable method to measure VAT.
Introduction

Adipose tissue generally considered a useful annex to provide protection, heat, and energy, has surpassed these activities, and as its study progresses it has positioned itself as an organ with neuroimmune-endocrine functions. Through the production of molecules such as hormones, antimicrobials, cytokines, and adipokines, it participates in the function of various cells and organs, which allows it to intervene in the defense and homeostasis of the body. Fat deposits are different from each other, even between those of the same type of adipose tissue. Each one is complex, made up of different cells, with different functions and variations both in gene expression and in their response to hormones (the subcutaneous of the thighs responds to sex hormones, the neck, upper back and abdomen to corticosteroids) [1].

Visceral adipose tissue (VAT) is divided into omental or epiploic and mesenteric. It occupies the spaces between the abdominal organs and keeps them in place. It has lymph nodes and a greater number of blood vessels and adrenergic receptors than the rest of the white adipose tissue. Adipocytes in visceral tissue also express a greater number of receptors for corticosteroids, and in obesity, the enzyme 11 beta-hydroxysteroid dehydrogenase is overexpressed, which generates active substances from inactive glucocorticoids, stimulating adipogenesis and increase visceral fat. Therefore, visceral adipose tissue has a greater relationship with the genesis of the metabolic syndrome and the pathology associated with obesity [2, 3].

The most accurate way to measure visceral fat level is with a computerized tomography (CT) or magnetic resonance imaging (MRI) scan. But without doubt, the most practical and simple way that will allow us to also measure many other parameters with greater or lesser precision depending on their quality is through a bioimpedance scale. Our body is normally made up of 50% to 70% water. Fat tissue barely has 10% so it is a worse conductor, generating resistance to the passage of electricity. This fact is used by bioimpedance scales to measure the time it takes for the electricity to pass through our body. Considering our weight, age and race, the percentage of body fat, visceral and bone density may be calculated.

Objectives

- To know the total and average visceral fat composition in a cohort of patients with moderate-severe psoriasis treated with biological therapy in a tertiary hospital using a bioimpedance scale.
- Establish the correlation of visceral adipose tissue with the body mass index (BMI) of the patients that make up this cohort.
- Establish if there is a relationship with the number of treatments and, therefore, refractoriness to them in patients with moderate-severe psoriasis.

Methods

A cross-sectional study of patients with moderate-severe psoriasis in the Psoriasis Unit of the San Cecilio University Hospital in Granada in the period July 1, 2020 - December 31, 2020 was performed. Patients were obtained by consecutive sampling. All patients signed an informed consent that they could revoke at any time during the study. The study is approved by the Ethics Committee of our hospital with code HUSC-DER-005.

The diagnosis of moderate-severe psoriasis was established when the patient met the following requirements (Psoriasis Area Severity Index [PASI] > 10, Body Surface Area [BSA] > 10 and / or Dermatology Life Quality Index [DLQI] > 10). All the patients were receiving biological therapy to control the disease.

The variables measured included age, sex, time since diagnosis, weight, height, BMI, visceral and total fat, and severity parameters (PASI, BSA, DLQI). All previous treatments that the patient had received, including systemic treatments and biological treatments, were considered. Treatment with biologically effective UVB phototherapy was excluded as a treatment to consider. Only the overall number of treatments was considered in those patients where the cause of switching was a primary or secondary failure, excluding safety reasons.

The visceral fat index was evaluated using a bioimpedance scale (Kanthor®), considering a cutoff point for a healthy level < 12 [4, 5].

The statistical software IBM SPSS version 25 in its macOS version was used for all analyses. The Kolmogorov Smirnov test was used to test the normality of the data. Measures of central tendency and dispersion were used depending on the nature of the data. Outcome variables were selected according to clinical criteria. The visceral fat variable was categorized according to the healthy cutoff point < 12 in a binomial variable for the analyses. Spearman correlation test for non-parametric samples as well as the Mann-Whitney U test for independent samples were used to study the association and relationship between the variables collected. A statistical significance level of P < 0.05 was set.

Results

Our sample consisted of 110 patients with a mean age of 47.47 years, with a clear predominance of males (61.7% of patients). The whole sample was placed to the right of the cutoff point considered as pathological in relation to the determination of visceral fat. The rest of the characteristics evaluated are reported in Table 1.

After testing for normality using the Kolmogorov-Smirnov test, the Mann-Whitney U Test for nonparametric data for independent samples was used, which revealed significant
Table 1. Clinical and anthropometric characteristics of the participants.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.47 ± 13.47 years</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (61.7)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (38.3)</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>22.84 ± 12.81 years</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.79 ± 21.00</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.1</td>
</tr>
<tr>
<td>BMI</td>
<td>28.49 ± 6.10</td>
</tr>
<tr>
<td>Visceral Fat</td>
<td>11.97 ± 7.30</td>
</tr>
<tr>
<td>Total Fat</td>
<td>29.02 ± 11.36</td>
</tr>
<tr>
<td>PASI</td>
<td>12.93 ± 5.23</td>
</tr>
<tr>
<td>BSA</td>
<td>15.18 ± 7.42</td>
</tr>
<tr>
<td>DLQI</td>
<td>11.72 ± 4.66</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation or n (%), as appropriate.

Table 2. Bivariate correlations between number of previously treatments and anthropometric variables.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gender</th>
<th>BMI</th>
<th>Total Fat</th>
<th>Categorised Visceral Fat</th>
<th>Number of previously treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>0.015</td>
<td>0.411**</td>
<td>0.180*</td>
<td>0.087</td>
<td>-0.023</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>-0.231*</td>
<td>-0.392**</td>
<td>-0.433**</td>
<td>0.119</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>0.411**</td>
<td>-0.231*</td>
<td>0.691**</td>
<td>0.629**</td>
<td>-0.059</td>
</tr>
<tr>
<td>Total Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorised visceral fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of previously treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.205*</td>
</tr>
</tbody>
</table>

Spearman correlation coefficient. *Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level.
metabolic syndrome in patients with psoriasis but with an abdominal fat index similar to the control group [9]. As in our study, in this case with an imaging technique, the authors were unable to establish a relationship between visceral fat levels and other markers related to metabolic syndrome.

Finally, studies have also been conducted using 18F-Fluorodeoxyglucose positron-emission tomography to measure VAT volume and its relationship with vascular inflammation in patients with psoriasis. It shows how new treatments for moderate-severe psoriasis lower the volume of VAT and vascular inflammation, which is why VAT is an important CV biomarker [10].

Our study has some limitations. It is a cross-sectional study, which has measured the visceral fat of our patients at a specific and determined moment. Although there is indeed a statistically significant correlation between the number of previous biological treatments (used due to refractoriness to treatment) and the levels of visceral fat, we have not been able to detect an association with other characteristics that have been used as biomarkers and prognoses factors in metabolic syndrome such as BMI. Furthermore, we have not been able to establish a correlation with imaging techniques already used in other studies due to the lack of availability of these techniques in our centre.

As a conclusion to our study, we want to value the determination of VAT using bioimpedance scales in patients with moderate-severe psoriasis. Further studies are required to determine its correlation with other characteristics of the disease and its positioning in relation to its determination using other imaging techniques already discussed.

References

Significance of Primary Melanoma Regression on Local Infiltrate and Outcome

Awatef Kelati1,2, Brigitte Balme3, Brigitte Chouvet3, Alexandra Traverse-Glehen3, Juliette Tantot3, Olivier Harou3, Gérard Duru4, Sebastien Debarbieux1, Stephane Dalle1,5,6, Luc Thomas1,5,6

1 Dermatology Department, Hôpital Universitaire Lyon Sud, Hospices Civils de Lyon. Pierre-Bénite, France
2 Dermatology Department, Cheikh Khalifa International University Hospital, Mohammed VI University of Health Sciences (UM6SS), Casablanca, Morocco
3 Anatomo-Pathology Department, Hôpital Universitaire Lyon Sud, Hospices Civils de Lyon. Pierre-Bénite, France
4 Research director in the Claude Bernard University, Lyon, France
5 Lyon 1 University Lyon France
6 Lyon Cancer Research Center, Centre Léon Bérard Lyon France

Key words: primary melanoma, local infiltrate, outcome, histopathology, dermoscopy

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Competing interests: None.

Authorship: All authors declare that they have sufficiently participated in the submitted work; all have had access to clinical material and have revised the manuscript before submission. Study concept and design: AK, BB, SD, and LT; Data acquisition, data analysis and interpretation, critical revision of the manuscript, and intellectual input: all authors; Drafting of manuscript: AK, BB, OH, SD, and LT; Statistical analysis: GD.

Corresponding author: Awatef Kelati, MD, Dermatology Department, Cheikh Khalifa International University Hospital, Mohammed VI University of Health Sciences (UM6SS), Casablanca, Morocco. E-mail: awatkelati@gmail.com

ABSTRACT

Introduction: The characteristics and the prognostic value of regression in primary melanomas are controversial.

Objectives: To further characterize “hot” and “cold” tumor’s stromas and to investigate the association between dermoscopy, pathology, and the prognostic implications of regression.

Methods: A 14-year-collection-based retrospective analysis was carried out on 40 patients with confirmed regressive melanomas.

Results: The extent of regression in dermoscopy was associated with the stage of the regression (P = 0.05) and with the MelanA patterns in histology (P = 0.02). Blue-gray and gray-brown color of the peppering (P = 0.01), and the eccentric, multifocal character of the dermoscopic regression (P = 0.05) were associated with “hot” stromas (CD8+, Granzym B+). Focal histologic regression (regressing melanomas) was associated with a good outcome (P < 0.001), while a complete regression (regressed melanomas) was associated with melanoma-related death (P < 0.001). “Hot” stromas (CD8+ were
significantly associated with survival at 10 years (P = 0.044), while “hot” stromas (Granzyme B+) were associated with the locoregional extension (P = 0.016), and the initial distant metastasis (P = 0.016).

Conclusions: Dermoscopic features of regression in primary melanomas were associated with the stage of regression, its extent, and the “hot” or “cold” nature of the tumor stroma, with prognostic implications.

Introduction

Histopathological features of regression, encountered in 10%-35% of primary cutaneous melanomas [1,2], classically appear on dermoscopy as white (or blue-white) scarlike areas (WSA) [3,4], variably admixed with blue-gray granularity (BGG) or “peppering”. Both WSA and BGG are unspecific features of regression, and are often regularly distributed on more than 50% of the surface benign lesions, while they are smaller and irregularly distributed in melanomas [3–6]. Recently, reticulated regression has been described in situ or slow-growing invasive melanomas as a new dermoscopic feature of regression, and appears as a coarse blue-gray net, with thick gray-blue lines with large pink-colored holes [2,7]. Although classic histopathological features of primary melanoma regression have been described over the past decades, their clinical implications and prognostic value remain unclear and controversial [2,8–16].

New interest in the evaluation of the nature of the host response, and the subsequent regression features in malignant tumors, especially melanomas, came after the development of immunotherapy. Tumor stromas have been sub-classified into “hotly” and “coldly” infiltrated by immune cells [17], with the pathogenic hypothesis that “hot” tumors may respond better to immunotherapy, which stimulates the already present immune cells, whereas “cold” tumors should (or could) be initially stimulated by specific neo-adjuvant agents before the initiation of immunotherapy.

Objectives

The primary aim of the present study was to further characterize “hot” and “cold” stromas in regressive melanomas based on dermoscopic and histopathologic criteria, and to preoperatively analyze dermoscopic features at different stages of regression. The secondary aim was to investigate the association between dermoscopy, pathology, and the prognostic implications of regression, with the ultimate goal of helping in the pre-therapeutic definition of “hot” tumors, which may benefit from postoperative adjuvant immunotherapy, and “cold” tumors, which could be included in potential neo-adjuvant clinical trials in priority before the excision of the primary tumor.

Methods

The present study was approved by the Hospices Civils de Lyon ethics committee, project N°20-15 (2019). It is a collection-based retrospective study of a consecutive series of patients having cutaneous melanomas with both confirmed dermoscopic and histopathological changes of regression, over a period of 14 years (2006-2019), for whom a complete set of clinical dermoscopic photographs was available. All patients gave their written informed consent for the use of their clinical records, clinical and dermoscopic images, pathological specimen at the time of the primary excision of the tumor, and subsequent inclusion in the Centre de Ressources Biologiques (Institutional biobank) of the Hospices Civils de Lyon for research purposes.

This study has not been registered in a public trial registry because it does not prospectively assigns human subjects to intervention or comparison groups to evaluate the cause and effect relationship between a medical intervention and a health outcome. This study does not fall into the scope of the French Jardé law, of 16th November 2016 because it uses a preexisting cohort of patients and preexisting clinical records.

The exclusion criteria were the absence or the poor quality of the dermoscopic images and the non-confirmation of the presence of histopathological features of regression upon reevaluation of the original histopathological slides. Clinical history, clinical and dermoscopic images, histopathological reports, standard immunochemistry data (MelanA), and, when applicable, genotyping of BRAF mutations were directly collected from patient electronic records.

Dermoscopic images were analyzed by 3 independent experienced dermatosists. Regression-associated features were recorded as well (WSA and BGG), and were specifically evaluated for their presence, their disposition (central, eccentric, unifocal, multifocal), and their surface extension (on less than 25%, between 25% and 50%, or on more than 50% of the lesion). The presence or absence of reticular regression was also recorded.

Histopathological and MelanA slides were evaluated independently by 4 dermatopathologists with no knowledge of the original histopathology report; the regression was sub-classified into 3 stages as reported in the literature [2]. Stage 1, or “inflammatory phase”, is characterized by a still recognizable tumor, with dense lymphocytic infiltrates admixed with nests of malignant melanocytes. Stage 2 or “regressing phase” is characterized by still recognizable...
melanoma cells, with tumor reduction or disappearance in the overlying epidermis, while in the papillary dermis the malignant tissue is replaced by lymphocytes and fibrosis. An increased vascularity is also observed because of angiogenesis, and heavily pigmented macrophages can be observed. Stage 3 or “regressed melanoma” is characterized by the complete disappearance of the tumor that is replaced by a dense fibrotic tissue with vessels and melanophages in varying numbers, with few or no lymphocytes underneath a thinned epidermis. The extent of regression was also examined, and classified as focal if it involved a portion of the dermal component of the tumor, partial if it involved the entire dermal component, and complete if it involved the entire tumor [2].

Additional immunophenotypic studies (CD8, Langerin, Granzyme B, and PDL-1) and an Orcein stain were performed on formalin-fixed paraffin-embedded original pathological specimens. The proportion (%) of cells positive for CD8, Granzyme B, Langerin, and PDL-1 was evaluated in the area of the regression and in the tumor stroma, and categorized as covering < 5%, ≥5 and <10%, ≥10 and <25%, ≥25 and <50%, ≥50 and >75%, or >75% of the whole inflammatory infiltrate. After discussion between the authors and a review of all the slides, tumors were considered as “hot” if their stroma was CD8+ on more than 25%, Granzyme B+ on more than 10% of the inflammatory infiltrate, PDL-1+ on more than 5%, or Langerin+ on more than 5%. Otherwise, they were considered as “cold”.

Following our clinical practice, BRAF mutation was tested only for primary tumors thicker than 1.00 mm.

Statistical Analysis
Analyses were performed using the Statistical Package for the Social Studies software version 20. Quantitative variables were expressed as mean (± standard deviation, SD) and qualitative variables as count (percentage). Progression-free survival was defined as the number of months from the diagnosis to the identification of locally recurrent or metastatic disease in the lymph nodes or distant organs. Death was considered as melanoma-related in patients for whom the melanoma had progressed. A univariate analysis was performed to investigate the association between histological regression characteristics, inflammatory infiltrate status, and prognosis, using a chi-squared test. A P value ≤0.05 was considered as significant.

Results
Among the 98 patients from the collection database, only 40 were included (30 were excluded because of incomplete dermoscopy record, 28 were excluded because of the absence of clear-cut histopathological features of regression). The mean (SD) age of included patients was 63.6 (15.7) years, and 82.5% of them presented with melanomas in the local stage (I and II of the AJCC 2018 Melanoma staging; Table 1).

Within the regression area of the tumor, WSA were observed in 55% of lesions, blue-WSA in 45%, BGG in 97.5% (Figures 1-3). Reticular regression was observed in 75% of cases, and was associated with the polychromatic character of the lesion (P = 0.047) and the stage 2 of the regression in histology (P = 0.049).

Table 1. Descriptive Analysis of Patients Included in the Present Study

<table>
<thead>
<tr>
<th>Total population n = 40</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>63.6 (15.7)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Dermoscopic regression</td>
<td>variables</td>
</tr>
<tr>
<td>Blue-white areas</td>
<td></td>
</tr>
<tr>
<td>Blue-white</td>
<td>18 (45)</td>
</tr>
<tr>
<td>White</td>
<td>22 (55)</td>
</tr>
<tr>
<td>Blue–white areas</td>
<td></td>
</tr>
<tr>
<td>Central Coverage of the lesion</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Eccentric</td>
<td>37 (92.5)</td>
</tr>
<tr>
<td>Less than 25%</td>
<td>14 (35)</td>
</tr>
<tr>
<td>25-50%</td>
<td>10 (25)</td>
</tr>
<tr>
<td>More than 50%</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Peppering</td>
<td>39 (97.5)</td>
</tr>
<tr>
<td>Focal</td>
<td>37 (92.5)</td>
</tr>
<tr>
<td>Total</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Table 1 continues
**Table 1. Descriptive Analysis of Patients Included in the Present Study (continued)**

<table>
<thead>
<tr>
<th>Total population n = 40</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color of the lesion</strong></td>
<td></td>
</tr>
<tr>
<td>Brown-gray</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Grey-blue</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Grey-blue and brown-gray</td>
<td>12 (30)</td>
</tr>
<tr>
<td><strong>Reticular regression in less palpable area</strong></td>
<td></td>
</tr>
<tr>
<td>Grey-blue lines</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Brown-gray lines</td>
<td>10 (25)</td>
</tr>
<tr>
<td><strong>Vascularization</strong></td>
<td></td>
</tr>
<tr>
<td>Polymorphic vessels</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Linear irregular</td>
<td>2 (5)</td>
</tr>
<tr>
<td><strong>Histopathology and immunochemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Melanoma histological subtype</td>
<td></td>
</tr>
<tr>
<td>SSM</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Regressive unclassifiable</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>LM</td>
<td>6 (15)</td>
</tr>
<tr>
<td>ALM</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Stage of the regression</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>2</td>
<td>24 (60)</td>
</tr>
<tr>
<td>3</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Extent of regression</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Focal</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>Partial</td>
<td>12 (30)</td>
</tr>
<tr>
<td>MelanA</td>
<td></td>
</tr>
<tr>
<td>Normal (stage 1 of regression)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Reduced in the dermis, reduced in the epidermis</td>
<td>26 (65)</td>
</tr>
<tr>
<td>Absent in the dermis, reduced in the epidermis</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Orcein in the regression area</td>
<td></td>
</tr>
<tr>
<td>Repressed, condensed, horizontal</td>
<td>35 (87.5)</td>
</tr>
<tr>
<td>Repressed, not condensed, horizontal</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Immunochemistry (Hot stromas)</td>
<td></td>
</tr>
<tr>
<td>CD8+</td>
<td>37 (92.5)</td>
</tr>
<tr>
<td>Granzyme B+</td>
<td>22 (55)</td>
</tr>
<tr>
<td>Langerin +</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>PDL1+</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Mutation BRAF V600 E</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Melanoma staging AJCC 2018</td>
<td></td>
</tr>
<tr>
<td>I and II (local)</td>
<td>33 (82.5)</td>
</tr>
<tr>
<td>III (loco-regional)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>IV (Metastatic)</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Evolution after 2 years of treatment</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Stable without clinical or radiologic evolution</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Complete remission after more than 2 years</td>
<td>30 (75)</td>
</tr>
</tbody>
</table>

SSM=Superficial spreading melanoma  
LM: Lentigo maligna  
ALM=Acral lentiginous melanoma  
AJCC =American Joint Committee on Cancer
Peppering was associated with thin melanomas (< 1mm, \(P = 0.012\)) and positive BRAF mutations (\(P = 0.028\)). WSA were associated with follicular migration in histology (\(P = 0.014\)). The extent of regression in dermoscopy was associated with the stage of regression (\(P = 0.05\)) and to MelanA patterns in histology (\(P = 0.023\)). Chaotic lesions were associated with stage 1 and 2 of regression (\(P = 0.035\)), irregular thick reticular lines (\(P = 0.049\)) and blue white veil (\(P = 0.014\)) were associated with stage 2 of regression. Annular granular pattern was associated with stage 2 and 3 of regression (\(P = 0.009\)). Skin fissures exaggeration in dermoscopy (\(P < 0.001\)), the presence of eccentric globules (\(P = 0.027\)), blue-white area
veil (P = 0.038), and perifollicular circles (P = 0.045) were associated with focal regression in histology. The loss of normal elastic fiber architecture in Orcein stain was associated with the WSA with peppering (P = 0.001; Table 2).

On the other hand, red milky areas (P = 0.033), irregular thick reticular lines (P = 0.044), polygones (P = 0.044), and blue-gray and gray-brown color of the peppering granules (P = 0.011) were associated with “hot” Granzyme B+ tumors, while “hot” CD8+ stromas were associated with skin fissures exaggeration (P = 0.043) and with the eccentric and multifocal character of regression in dermoscopy (P = 0.05). “Cold” PDL1+ stromas were associated with inversed network in dermoscopy (P = 0.05) and eccentric globules (P = 0.044), while “cold” Langerin+ stromas were associated with the multicomponent pattern (P = 0.032), peripheral structureless area (P = 0.026), and the rhomboidal pattern (P = 0.049) (Table 2).

**Table 2. Univariate Analysis**

<table>
<thead>
<tr>
<th>Variables</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodepression</td>
<td>Stage 3 of regression 0.000</td>
</tr>
<tr>
<td>Elevated lesion (plaque ou nodular)</td>
<td>Hot stroma Granzyme B+ 0.038</td>
</tr>
<tr>
<td>Lesion color (polychromatic or achromatic)</td>
<td>BRAF mutation 0.035</td>
</tr>
<tr>
<td>Regression extent</td>
<td>0.041</td>
</tr>
<tr>
<td>Reticular regression in an area less palpable than the other areas</td>
<td>0.014</td>
</tr>
<tr>
<td>Loco-regional metastasis</td>
<td>Dermoscopic regression (Blue-white areas (scar like)) 0.041</td>
</tr>
<tr>
<td></td>
<td>Focal regression in histology 0.004</td>
</tr>
<tr>
<td></td>
<td>Hot stroma Granzyme B+ 0.016</td>
</tr>
<tr>
<td>Peppering</td>
<td>Focal regression (focal peppering) 0.000</td>
</tr>
<tr>
<td></td>
<td>Low risk of recurrence after complete remission after surgery 0.029</td>
</tr>
<tr>
<td>Extent of regression in dermoscopy</td>
<td>MelanA expression 0.023</td>
</tr>
<tr>
<td></td>
<td>Regression stages in histology 0.05</td>
</tr>
<tr>
<td></td>
<td>Hot stroma CD8+ 0.05</td>
</tr>
<tr>
<td>Granules color</td>
<td>Hot stroma Granzyme B+ 0.011</td>
</tr>
<tr>
<td>Reticular type of regression</td>
<td>Regression stage 2 0.049</td>
</tr>
<tr>
<td>Annular granular pattern</td>
<td>Stage 2 and 3 of regression 0.009</td>
</tr>
<tr>
<td></td>
<td>Good outcome with complete remission, and no evolution after treatment 0.001</td>
</tr>
<tr>
<td>Irregular thick reticular lines</td>
<td>Stage 2 of regression 0.049</td>
</tr>
<tr>
<td></td>
<td>Hot stroma Granzyme B+ 0.044</td>
</tr>
<tr>
<td>Skin fissures exaggeration</td>
<td>Focal regression in histology 0.000</td>
</tr>
<tr>
<td></td>
<td>Hot stroma CD8+ 0.043</td>
</tr>
<tr>
<td></td>
<td>Good outcome with complete remission, and no evolution after treatment 0.002</td>
</tr>
<tr>
<td></td>
<td>Good response to immunotherapy 0.003</td>
</tr>
</tbody>
</table>

Table 2 continues
Focal regression was associated with good outcome (P < 0.001) and the immunotherapy response (P < 0.001), while complete and partial regression of histology were associated with melanoma-related death (P < 0.001), regression stage 3 of histology was associated with melanoma-related death at both 2 years (P = 0.048) and 5 years (P = 0.020) since initial treatment. “Hot” CD8+ stromas were associated with a good response to immunotherapy (P = 0.032), and with the survival at 10 years (P = 0.044). Also, “hot” Granzyme B+ stromas were associated with locoregional extension (P = 0.016), and initial distant metastasis (p=0.016) (Table 2).

The local extension (in transit metastasis) of these regressive melanomas was associated with the stage 2 of regression (P = 0.030), while locoregional extension and initially distant metastasis were associated with WSA in dermoscopy (P = 0.041) and with focal regression in histology (P = 0.008; Table 2).

Conclusions

In the present study we were able to further characterize “hot” and “cold” stromas in the context of melanoma regression based on dermoscopic criteria and the inflammatory infiltrate status. Indeed, we found an association of many and specific dermoscopic features with “hot” Granzyme B+ and “hot” CD8+ stromas, or “cold” PDL1+ and “cold” Langerin+ stromas. This further characterization of the previous sub-classification of “hot” and “cold” stromas in melanomas [17] based on the immunopathology nature of the inflammatory infiltrate had interesting prognostic implications, as CD8+ stromas were significantly associated with a good response to immunotherapy, and to the disease free survival at 10 years, which confirms a study that has previously reported an association between CD8 T-cell infiltration and better prognosis [14]. Also, “hot” Granzyme B+ stromas were associated with locoregional extension and the initial distant metastasis, while no prognostic implication of Langerin or PDL-1 expression around the tumor and in the regression were found in the present study. The prognostic value of PDL-1 is controversial, as some authors have failed to observe a correlation between PDL-1 expression in sentinel lymph node metastases and the outcome (which is consistent with our results), while others have reported PDL-1 as an independent negative prognostic marker in conventional melanoma, and, in contrast, others have reported PDL-1 expression in mucosal melanomas as correlated with longer recurrence-free survival [18].

A preoperatively comparison of various dermoscopic features of regressive melanoma at different stages of regression was made, and the association between dermoscopy, pathology, and the prognostic implications of regression was investigated. Peppering was found as significantly associated with thin melanomas in histology, this refines knowledge about peppering that has been described as an expression of melanophages in the dermis [2], and has been significantly associated with BRAF mutation [2], confirming that regression may be a hallmark of BRAFV600 melanomas. In addition, in primary melanomas, mutated BRAF has been
described as an adverse prognostic factor [20]. In the present study, even though BRAF mutation status was not found in many patient records because most had thin melanomas, it was significantly associated to rapidly growing melanomas, which were polychromatic, chaotic, or with a multicomponent pattern in dermoscopy, or with signs of horizontal growth and local extension. As a result, BRAF mutation may be a prognostic factor in regressive melanomas. Also, the dermoscopic extent of regression (WSA with peppering) was significantly associated with regression stages in histology and enabled us to evaluate the aggressiveness of the tumor, since the results presented herein demonstrated an association between advanced stages of regressive melanomas and the extent of regression, and between stage III melanoma and melanoma-related death. In addition, the presence of dermoscopic signs associated with hot stromas CD8+ or Granzyme B+ (red milky areas, irregular thick reticular lines, polygons, the peppering granules’ color, and the eccentric, multifocal character of regression), supports the idea that further dermoscopic investigations of the regression in primary melanomas would be of great help in the pre-excision therapeutic evaluation and predictable therapeutic response.

Reticular regression in a clinically less palpable area, which has been recently reported [7,19], was frequent in patients who had stage 2 of regression in thin melanomas. This type of regression may be correlated with the remaining junctional component and the heterogeneous dermal regression in stage 2 before the complete disappearance of the dermal tumor.

Remarkably, MelanA red immunostaining could be a good tool to confirm, characterize, and probably classify the histologic regression, especially when histologic regression is not so obvious. Despite contradictions in the literature, patients with thin melanomas who show partial regression cannot be included in the “low-risk” group if the extent of regression is more than 50% [16,21,22]. Completely regressive lesions represent a factor of delay in diagnosis, and of development of locoregional and distant metastasis, as it has been reported in some case reports and studies [21,23]. This was also confirmed with the results herein as melanoma-related death was associated with regressed melanomas (stage 3 and complete regression).

The data herein suggest that the prognostic role of regression depends on the stage of melanoma, the stage of regression and its extent (regressing or regressed melanomas), and the “hot” or “cold” nature of the CD8+ and Granzyme B+ tumor stroma, which may explain the controversies found in the literature concerning regression [2] as it has not been precisely sub-classified previously.

Due to the retrospective nature of this study, many important data were missing from the patient records: for example, the BRAF status that was not determined for all patients, especially because most melanomas were thin, it was therefore not possible to draw conclusions about the prognostic value of BRAF mutation in regressive melanomas. However, even though this aspect would have been interesting to determine, and for future studies, it was not among our main objectives. Also, the small number of patients was due to the retrospective collection of the records and to the dermoscopic images themselves that were often not found or of poor quality, leading to the exclusion of some patient. Additionally, some patients were excluded after review by experienced pathologists because regression was not objectively observed.

The present study provides a better characterization of regression in primary melanomas, and a better comprehension of the “hot” or “cold” character of the stroma. An important outcome of the study is that regressing melanoma (early stages of regression) is associated with favorable outcome whereas regressed melanoma (complete regression stage 3) is associated with a worse outcome. Further studies with a prospective design could help in confirming and investigating these results, especially the importance of dermoscopy in predicting the immunophenotypic host response, with the ultimate goal to help in the pre-therapeutic definition of “hot” tumors that may benefit of postoperative adjuvant immunotherapy, and “cold” tumors in which inclusion in potential neo-adjuvant clinical trials could be proposed in priority before excision of the primary tumor.

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We are grateful to Hélène Boyer and Philip Robinson (Direction de la Recherche Clinique et de l’Innovation, Hospices Civils de Lyon) for their help to improve the manuscript.

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References


Extrafacial Lentigo Maligna: A Clinical And Dermoscopic Analysis According to Localization

Gabriel Salerni¹, Emilia Cohen-Sabban², Horacio Cabo³

¹Dermatology Department, Hospital Provincial del Centenario de Rosario, Universidad Nacional de Rosario, Diagnóstico Médico Oroño, Rosario, Argentina
²Dermatology Service, Instituto de Investigaciones Médicas Alfredo Lanari, Universidad de Buenos Aires, Argentina
³Dermatology Department, Universidad de Buenos Aires, Argentina

Key words: skin cancer, melanoma, lentigo maligna, dermoscopy


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Corresponding author: Gabriel Salerni, MD, Dermatology Department, Hospital Provincial del Centenario de Rosario - Universidad Nacional de Rosario - Diagnóstico Médico Oroño, Rosario, Argentina. Email: gabrielsalerni@hotmail.com

ABSTRACT

Introduction: Whether extrafacial lentigo maligna (EFLM) differs clinically and/or dermoscopically according to location has not been analyzed in depth.

Objectives: To evaluate clinical and dermoscopic characteristics regarding different localization in a series of EFLM.

Methods: We conducted a retrospective analysis of clinical and dermoscopic characteristics of 69 histologically proven EFLM retrieved from the database of two private institutions.

Results: Of the 69 EFLM included in the study, 25 (36.2%) were located in posterior trunk (PT), 16 (23.2%) in anterior trunk (AT), 15 (21%) in upper extremities (UE), and 13 (18.8%) in lower extremities (LE). Mean diameter among localization were as follows: 14.3 mm in PT, 11.8 mm in AT, 14 mm in UE, and 10 mm in LE (p 0.44). The most frequent dermoscopic criteria were angulated lines and tan structureless areas (70%), followed by atypical pigment network (60%), both with similar distribution among groups. Angulated lines pattern was the most frequent global pattern, observed in 55% of cases. Tan structureless/granularity pattern and patchy peripheral pigmented islands pattern were seen in 15.6% and 11.6% cases, respectively. No statistically significant differences were observed in the distribution of global dermoscopic pattern in the different localizations.

Conclusions: From the clinical point of view, EFLM did not differ in terms of patient’s age and diameter regarding localization. Upon dermoscopy, we found no significant differences in the overall dermoscopic pattern in the different localizations.
Introduction

Lentigo maligna (LM) is a variant of *in situ* melanoma that develops mainly in chronic sun exposure areas in middle-aged and elderly patients. If left untreated, it can evolve to its invasive form, LM melanoma [1]. Hence, early recognition and proper management is crucial to reduce morbidity and mortality associated to melanoma.

Dermoscopy has shown to increase the sensitivity and specificity in the clinical diagnosis of melanoma by allowing the visualization of diagnostic criteria not visible to naked eye. Moreover, its routine use for the evaluation of melanocytic and non-melanocytic skin lesions is recommended in most of the clinical guidelines worldwide [2,3]. Dermoscopic criteria such as granularity, angulated lines, or vessels as well as overall dermoscopic patterns have been described to improve recognition of lentigo maligna in nonfacial chronically sun-damaged skin [4].

Objectives

We sought to evaluate clinical and dermoscopic characteristics regarding different localization in a series of extrafacial lentigo maligna (EFLM) confirmed by histopathology.

Methods

We conducted a retrospective analysis of clinical and dermoscopic characteristics of 69 histologically proven EFLM diagnosed between 2016 and 2020 in two private clinics. The study included primary LM with clinical and dermoscopic pictures of acceptable quality to allow reliable evaluation. Dermoscopic images were captured with polarized light using hand-held dermatoscope (Dermlite II pro Hybrid, 3Gen LLC) attached to a digital camera and digital dermoscopy devices (FotoFinder Systems GmbH).

The study was conducted according to the Declaration of Helsinki; patient’s written consent was obtained for all invasive procedures.

Epidemiological data such as age and gender of the patients and clinical data the localization and diameter of the lesions were incorporated along with the clinical and dermoscopic images in a PowerPoint presentation (Microsoft Corp). This collection was presented to 2 dermatologists with experience in dermoscopy (G.S. and H.C.) who performed both clinical and dermoscopic evaluation. Dermoscopic images were assessed for the presence or absence of criteria for melanoma previously described in nonfacial skin [4-6].

Statistical Analysis

The $\chi^2$ test was used to compare qualitative variables, and the $t$ test was used to compare means. Differences were set as statistically significant at $P \leq 0.05$.

Results

Of the 69 EFLM included in the study, 25 (36.2%) were located in posterior trunk (PT), 16 (23.2%) in anterior trunk (AT), 15 (21%) in upper extremities (UE), and 13 (18.8%) in lower extremities (LE).

Population

The study population consisted of 24 females (34.8%) and 45 males (65.2%), with a mean age of 68.5 years (range 38-86). No statistically significant differences were observed in age according to localization (Figure 1). Distribution according to gender was homogeneous among the 4 groups.

Clinical Evaluation

Mean diameter among localization were as follows: 14.3 mm (5-24 mm) in PT, 11.8 mm (6-23 mm) in AT, 14 mm (2-30 mm) in UE, and 10 mm (range 4-24 mm) in LE (Figure 2). No statistically significant differences were observed regarding diameter and localization ($P = 0.44$). EFLM in individuals older than 70 years showed a significantly greater diameter than in those younger than 70 years ($P = 0.002$).

In clinical examination (Table 1), 60 out of the 69 EFLM included (87%) were considered striking from the clinical point of view. Concerning localization, all lesions located in UE were considered clinically striking, 92% of the lesions in PT, 80% in AT, and 70% in LE, respectively. Light brown and dark brown were the most frequent colors, observed in about the 90% of the cases. White, blue-grey and pink were the less frequent colors observed clinically. Lesions located in AT displayed only
Figure 2. Diameter distribution is similar among localization categories (Kruskal-Wallis test, P = 0.44).

LE=lower extremities; UE=upper extremities; AT=anterior trunk; PT=posterior trunk

3 colors: light brown, dark brown and blue-grey, while in the other localizations at least 5 colors were observed.

Dermoscopic Evaluation

The dermoscopy evaluation findings are shown in Table 2. The most frequent dermoscopic criteria were angulated lines and tan structureless areas, observed in more than three quarters of all the EFLM analyzed, with quite similar distribution among the different localizations. Atypical pigment network was observed in 60% of all the EFLM, also with similar observation among groups. Hyperpigmented follicular pigmentation was observed in almost one third of the cases, being less frequent in PT. Aggregated dots were seen in less than 20% of the EFLM, being more frequent in AT. Blue-white veil and negative pigment network were observed in 6% of the cases; none of the EFLM displayed circle within circle criteria. Only 1 lesion located in TP showed radial projections.

Almost half of the EFLM showed regression structures: 36.2% granularity and 23.2% scar-like areas; regression structures were less frequent in LE.

Dotted and polymorphous vessels were the most frequent vascular pattern observed (15.9% and 11.6%, respectively). Serpentine vessels and milky-red areas were observed in 7% of all EFLM, with similar distribution among different localizations, but milky-red areas criterion was not observed in LE. None of the melanomas included showed red globules.

Near half of the EFLM displayed dermoscopic criteria for seborrheic keratosis, being more frequent in PT and UE, but no statistically significant differences were observed regarding localization.

The 6 colors were observed in all localizations upon dermoscopy. Light brown was observed in all cases, and dark brown in 66 out of 69 lesions. Blue-grey color was present in more than half of the lesions, with similar distribution regarding localization. Pink, white, and black colors were seen in near 40% of all EFLM. Pink and white colors were more frequent in PT and UE. Black color was more frequent in LE.

Global dermoscopic pattern analysis is shown in Table 3. Angulated lines pattern was the most frequent pattern, observed in 55% of cases. Tan structureless/granularity pat-

Table 1. Clinical Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Lower extremities n (%)</th>
<th>Upper extremities n (%)</th>
<th>Anterior trunk n (%)</th>
<th>Posterior trunk n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>13 (18.8)</td>
<td>15 (21.7)</td>
<td>16 (23.2)</td>
<td>25 (36.2)</td>
<td>69 (100)</td>
</tr>
<tr>
<td>Colors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light brown</td>
<td>11 (84.6)</td>
<td>14 (93.3)</td>
<td>15 (93.7)</td>
<td>23 (92)</td>
<td>63 (91.3)</td>
</tr>
<tr>
<td>Dark brown</td>
<td>12 (92.3)</td>
<td>13 (86.6)</td>
<td>13 (81.2)</td>
<td>24 (96)</td>
<td>62 (89.9)</td>
</tr>
<tr>
<td>Pink</td>
<td>3 (23)</td>
<td>3 (20)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>8 (11.6)</td>
</tr>
<tr>
<td>Blue-gray</td>
<td>1 (7.7)</td>
<td>2 (13.3)</td>
<td>2 (12.5)</td>
<td>0 (0)</td>
<td>5 (7.2)</td>
</tr>
<tr>
<td>White</td>
<td>0 (0)</td>
<td>1 (6.6)</td>
<td>0 (0)</td>
<td>2 (8)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (38.4)</td>
<td>5 (33.3)</td>
<td>0 (0)</td>
<td>7 (28)</td>
<td>17 (24.6)</td>
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<tr>
<td>Borders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ill defined</td>
<td>6 (46.1)</td>
<td>6 (40)</td>
<td>8 (50)</td>
<td>20 (80)</td>
<td>41 (59.4)</td>
</tr>
<tr>
<td>Well defined, irregular</td>
<td>5 (38.4)</td>
<td>9 (60)</td>
<td>7 (43.5)</td>
<td>5 (20)</td>
<td>26 (37.7)</td>
</tr>
<tr>
<td>Well defined, regular</td>
<td>2 (15.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Striking lesion</td>
<td>9 (69.2)</td>
<td>15 (100)</td>
<td>13 (81.2)</td>
<td>23 (92)</td>
<td>60 (87)</td>
</tr>
</tbody>
</table>
### Table 2. Dermoscopic Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Lower extremities n (%)</th>
<th>Upper extremities n (%)</th>
<th>Anterior trunk n (%)</th>
<th>Posterior trunk n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>13 (18.8)</td>
<td>15 (21.7)</td>
<td>16 (23.2)</td>
<td>25 (36.2)</td>
<td>69 (100)</td>
</tr>
<tr>
<td>Angulated lines</td>
<td>13 (100)</td>
<td>11 (73.3)</td>
<td>12 (75)</td>
<td>17 (68)</td>
<td>53 (76.8)</td>
</tr>
<tr>
<td>Aggregated dots</td>
<td>2 (15.4)</td>
<td>1 (6.6)</td>
<td>5 (31.2)</td>
<td>4 (16)</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>Atypical pigment network</td>
<td>8 (61.5)</td>
<td>8 (53.3)</td>
<td>10 (62.5)</td>
<td>15 (60)</td>
<td>41 (59.4)</td>
</tr>
<tr>
<td>Asymmetric peril follicular hyperpigmentation</td>
<td>5 (38.4)</td>
<td>7 (46.6)</td>
<td>7 (43.5)</td>
<td>2 (8)</td>
<td>21 (30.4)</td>
</tr>
<tr>
<td>Peripheral tan structureless areas</td>
<td>10 (76.9)</td>
<td>12 (80)</td>
<td>14 (87.5)</td>
<td>18 (72)</td>
<td>54 (78.3)</td>
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<tr>
<td>Negative network</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Circle within circle</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blue-white veil</td>
<td>1 (7.7)</td>
<td>1 (6.6)</td>
<td>1 (6.2)</td>
<td>1 (4)</td>
<td>4 (5.8)</td>
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<tr>
<td>Streaks</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pseudopods</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Radial projections</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1 (1.4)</td>
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<td>Vascular structures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dotted vessels</td>
<td>3 (23)</td>
<td>5 (33.3)</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>11 (15.9)</td>
</tr>
<tr>
<td>Serpentine vessels</td>
<td>1 (7.7)</td>
<td>3 (20)</td>
<td>1 (6.2)</td>
<td>1 (4)</td>
<td>6 (8.7)</td>
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<tr>
<td>Polymorphous vessels</td>
<td>2 (15.4)</td>
<td>3 (20)</td>
<td>1 (6.2)</td>
<td>2 (8)</td>
<td>8 (11.6)</td>
</tr>
<tr>
<td>Milky-red areas</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>1 (6.2)</td>
<td>2 (8)</td>
<td>5 (7.2)</td>
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<tr>
<td>Red globules</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>White shiny structures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiny white lines</td>
<td>2 (15.4)</td>
<td>2 (13.3)</td>
<td>1 (6.2)</td>
<td>2 (8)</td>
<td>7 (10.1)</td>
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<tr>
<td>White shiny areas</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Rosettes</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>Regression structures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absence</td>
<td>11 (84.6)</td>
<td>8 (53.3)</td>
<td>8 (50)</td>
<td>10 (40)</td>
<td>37 (53.6)</td>
</tr>
<tr>
<td>Granularity or peppering</td>
<td>2 (15.4)</td>
<td>5 (33.3)</td>
<td>7 (43.5)</td>
<td>11 (44)</td>
<td>25 (36.2)</td>
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<tr>
<td>Scar-like areas</td>
<td>0 (0)</td>
<td>4 (26.6)</td>
<td>3 (18.7)</td>
<td>9 (36)</td>
<td>16 (23.2)</td>
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<tr>
<td>Prominent skin markings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criteria for seborrheic keratosis</td>
<td>4 (30.7)</td>
<td>8 (53.3)</td>
<td>6 (37.5)</td>
<td>15 (60)</td>
<td>33 (47.8)</td>
</tr>
<tr>
<td>Colors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light brown</td>
<td>13 (100)</td>
<td>15 (100)</td>
<td>16 (100)</td>
<td>25 (100)</td>
<td>69 (100)</td>
</tr>
<tr>
<td>Dark brown</td>
<td>13 (100)</td>
<td>15 (100)</td>
<td>16 (100)</td>
<td>24 (96)</td>
<td>66 (98.6)</td>
</tr>
<tr>
<td>Pink</td>
<td>3 (23)</td>
<td>8 (53.3)</td>
<td>5 (31.2)</td>
<td>14 (56)</td>
<td>30 (43.5)</td>
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<tr>
<td>Blue-gray</td>
<td>7 (53.8)</td>
<td>9 (60)</td>
<td>9 (56.2)</td>
<td>12 (48)</td>
<td>37 (53.6)</td>
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<tr>
<td>White</td>
<td>3 (23)</td>
<td>7 (46.6)</td>
<td>5 (31.2)</td>
<td>12 (48)</td>
<td>27 (39.1)</td>
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<tr>
<td>Black</td>
<td>6 (46.1)</td>
<td>6 (40)</td>
<td>5 (31.2)</td>
<td>8 (32)</td>
<td>25 (36.2)</td>
</tr>
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</table>

### Table 3. Dermoscopic Patterns

<table>
<thead>
<tr>
<th></th>
<th>Lower extremities n (%)</th>
<th>Upper extremities n (%)</th>
<th>Anterior trunk n (%)</th>
<th>Posterior trunk n (%)</th>
<th>Total n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases per localization</td>
<td>13 (18.8)</td>
<td>15 (21.7)</td>
<td>16 (23.2)</td>
<td>25 (36.2)</td>
<td>69 (100)</td>
<td></td>
</tr>
<tr>
<td>Global dermoscopic pattern</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patchy peripheral pigmented islands</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>3 (18.7)</td>
<td>3 (12)</td>
<td>8 (11.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Angulated lines</td>
<td>8 (61.5)</td>
<td>7 (46.7)</td>
<td>7 (43.7)</td>
<td>16 (64)</td>
<td>38 (55.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>Tan structureless and granularity</td>
<td>2 (15.4)</td>
<td>1 (6.7)</td>
<td>4 (25)</td>
<td>4 (16)</td>
<td>11 (15.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>None</td>
<td>3 (23.1)</td>
<td>5 (33.3)</td>
<td>2 (12.5)</td>
<td>2 (8)</td>
<td>12 (17.4)</td>
<td>0.19</td>
</tr>
</tbody>
</table>
tern and patchy peripheral pigmented islands pattern were seen in the 15.6% and 11.6% of cases, respectively (Figure 3). Twelve of 69 lesions (17.3%) showed none of these global patterns. No statistically significant differences were observed in the distribution of global dermoscopic pattern in the different localizations.

Table 4. Number of Colors in the Clinical and Dermoscopic Examination

<table>
<thead>
<tr>
<th>Number of colors in clinical examination n (%)</th>
<th>Number of colors in dermoscopic examination n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 7 (10)</td>
<td>64 (92.7)</td>
</tr>
<tr>
<td>2 42 (60.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3 15 (21.7)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>4 2 (2.9)</td>
<td>23 (33.3)</td>
</tr>
<tr>
<td>5 3 (4.3)</td>
<td>21 (30.4)</td>
</tr>
<tr>
<td>6 0 (0)</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td></td>
<td>4 (5.8)</td>
</tr>
</tbody>
</table>

P < 0.001

Colors Upon Clinical versus Dermoscopic Evaluation

Table 4 shows number of colors observed upon clinical and dermoscopic examination. With the use of dermoscopy, the percentage of melanomas displaying at least 4 colors raised from 7.3% to 53.6% (P < 0.001)

Conclusions

LM is a distinct form of melanoma in situ, which is characterized by an increased number of histologically atypical melanocytes situated along the dermo-epidermal junction. It mainly develops in middle-age and elderly individuals on chronically sun exposed areas. Although LM can precede by many years the dermal invasion, rapid progression has been
described [7,8]. Therefore, early diagnosis and appropriate treatment are essential to improve prognosis. Whether EFLM differs clinically and/or dermoscopically according to location has not been analyzed in depth.

The clinical diagnosis of EFLM can be challenging since it can simulate other conditions especially solar lentigo or pigmented actinic keratosis. In our study, 90% of the EFLM were striking from the clinical point of view; the lesions were clinically polychromatic (at least 3 colors) and with a similar diameter regardless of location. Lesions tend to have a greater diameter in upper extremities and posterior trunk, but differences were not statistically significant.

Dermoscopy has become a key diagnostic tool to enhance both sensitivity and specificity in the clinical diagnosis of melanoma [2,3]. The dermoscopic criteria of LM and its invasive form, LM melanoma, were first described in facial location. Furthermore, a progression model for facial LM has been well established and has been widely accepted [9]. More recently, dermoscopic features of LM in extrafacial location were described [4-6]. In 2013, Keir reported that the global criterion of lentigo-like pigment pattern lacking a lentigo-like border, combined with the criteria of asymmetrically pigmented follicular openings and large polygons detected the great majority of melanoma in his series of 20 cases (18 in situ) [5]. Jaimes et al described and analyzed the clinical and dermoscopic characteristics of both in situ and invasive melanomas on nonfacial chronically sun-damaged skin; they concluded that outlier lesions manifesting dermoscopic structures, such as granularity, angulated lines, or vessels and any of the 3 described dermoscopic patterns: patchy peripheral pigmented islands, angulated lines pattern and tan structureless and granularity pattern should raise suspicion for melanoma.

In our series, peripheral tan structureless areas, angulated lines and atypical pigment network were the most frequent dermoscopic criteria observed. Angulated lines were more frequent in HE, where they were observed in all cases; conversely, tan structureless areas and atypical pigment network had similar distribution among different localizations. Asymmetric perifollicular hyperpigmentation was much less frequent in PT. Regression structures were more prevalent in PT. Aggregated dots were more frequent in AT, regression structures were more prevalent in PT, asymmetric perifollicular hyperpigmentation was much less frequent in PT, vascular structures were more frequent in UE, white shiny lines were more frequently observed in extremities than in the trunk. We found no significant differences in the overall dermoscopic pattern in the different localizations.

References


Isotretinoin Treatment Practices and Outcomes in Acne Patients During the COVID-19 Pandemic: A Single Center, Retrospective, Comparative Study

Mehmet Fatih Atak¹,², Banu Ismail Mendi², Incilay Kalay Yildizhan², Hatice Sanli², Banu Farabi³

¹ Dermatology Department, Tokat State Hospital, Tokat, Turkey
² Dermatology Department, Ankara University, Ankara, Turkey
³ Department of Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ, USA

Key words: Isotretinoin, treatment, acne, COVID-19, pandemic


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Corresponding author: Banu Farabi, Department of Internal Medicine, Saint Peter’s University Hospital, New Brunswick, NJ, USA.
E-mail: banufarabi91@gmail.com

ABSTRACT

Introduction: The COVID-19 pandemic drastically changed the priorities in healthcare services; outpatient management of acne has changed during this period.

Objectives: We aimed to investigate treatment practices, outcomes and identify modified follow-up schedules applied during the pandemic.

Methods: The patients who were admitted to dermatology outpatient clinic between March 13 and July 13, 2020, were included. Patients who were admitted between March 13 and July 13, 2019, were served as controls for the study. For each patient, age, gender, treatment protocols, treatment intervals, compliance with the treatment, treatment modifications, and adverse events were recorded.

Results: The total number of acne patients admitted to dermatology outpatient clinics during the pandemic period was 278 and consisted of 12.3% (278) of all admissions. Isotretinoin treatment was started in only 16 (5.8%) of the patients. The proportion of patients who were under follow-up was significantly higher during the pandemic period (P < 0.005). There was no difference between the pandemic period and the non-pandemic period in terms of starting isotretinoin treatment (P > 0.05). During pandemic period, 79% of the patients who used isotretinoin were followed-up every two or more months. Extended follow-up intervals showed no difference for detecting side effects (P > 0.05).
Introduction

COVID-19 pandemic affected the healthcare practices all over the world in 2020. It drastically changed the priorities in healthcare services, thus outpatient management of elective diseases such as acne have also been shaped during this period [1]. Restrictions and the fear of infection altered outpatient clinic patient profile in dermatology clinics and resulted implementation of teledermatology visits [2].

The effects of pandemic on dermatological practices have been investigated especially in chronic diseases treating with immunosuppressive or immunomodulatory drugs, but there are not enough studies focusing on the effects of acne and its management during the pandemic. Acne patients consist of an important part of the routine dermatology outpatient clinics, thus further studies are required to establish the management of acne [3].

Objectives

We aimed to investigate the treatment practices, treatment outcomes, adherence of acne patients and to identify modified follow-up schedules during the pandemic period.

Methods

The IRB approval for the study was obtained from the Ankara University Ethics Committee on April 2021. The patients visited the dermatology clinic between March 13 and July 13, 2020, when first restrictions were imposed by the Turkish government due to pandemic, have been retrospectively reviewed for the clinical diagnosis of acne vulgaris through electronic medical record system. A total number of 278 acne patients seen in our clinic for 4 months period during the pandemic was included in the study. For each patient age, gender, treatment protocols, treatment intervals, compliance with the treatment, adverse events were recorded. Patients were stratified according to age as follow: younger than 18 years of age, and 18 years or older. Treatment protocols were assessed in three categories as follows: topical treatment, systemic antibiotic treatment with topical treatments, and oral isotretinoin treatment. Treatment intervals were determined in two different categories as follows: monthly or in every two months or longer. Adverse events were recorded. The patients admitted in the outpatient clinic between March 13 and July 13, 2019, served as controls for the study.

Statistical analysis was performed using the SPSS 22.0 program. Mean, standard deviation and percentage were used for descriptive statistics. Chi-square test was performed to examine differences between categorical variables in same groups and the P value of less than 0.05 was accepted as statistically significant.

Results

The total number of patients admitted to outpatient clinic during pandemic period was 2265. Acne patients consisted of 12.3% (278) of all admissions. On the other hand, the total number of patients admitted to dermatology outpatient clinic during non-pandemic period was 7604 and 7.5% (577) were acne patients. The distribution of the patients according to the gender and age is shown in Table 1, and there was no significant difference between two periods according to gender and age (P > 0.05).

<table>
<thead>
<tr>
<th>Demographic characteristics of the acne patients</th>
<th>Pandemic period (n = 278)</th>
<th>Non-pandemic period (n = 577)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>179 (64.4%)</td>
<td>383 (66.4%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Female</td>
<td>99 (35.6%)</td>
<td>194 (33.6%)</td>
<td></td>
</tr>
<tr>
<td>Age, years (mean)</td>
<td>22.80 (SD ± 7.12)</td>
<td>22.16 (SD ± 6.98)</td>
<td>0.22</td>
</tr>
<tr>
<td>&lt; 18</td>
<td>64 (23%)</td>
<td>122 (21.1%)</td>
<td>0.53</td>
</tr>
<tr>
<td>&gt; 18</td>
<td>214 (87%)</td>
<td>455 (88.9%)</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation.
Table 2 summarizes the treatment modalities of the patients with the first admission and under follow-up in both pandemic and non-pandemic periods. Among the patients who applied to dermatology outpatient clinic during pandemic period, 124 (44.6%) had first admission and 150 (54%) were under follow-up for different acne treatments, and 4 of them were consultation patients. One hundred and sixteen (93.5%) patients with first admission did not receive treatment for acne previously, whereas 8 of them were under systemic treatments (oral isotretinoin n = 2, doxycycline n = 6). Of the 116 treatment naïve patients, topical treatment was given to 77 (n = 27.7%), oral isotretinoin treatment to 16 (5.8%) and systemic antibiotic treatment with topicals to 23 (8.3%) patients. Of the 8 patients taking systemic treatment at first admission, doxycycline treatment was switched to oral isotretinoin for 3 patients and to azithromycin for one patient, and the others continued their current systemic treatment (oral isotretinoin n = , doxycycline n = 2).

During the pandemic, 26 (9.4%) of the follow-up patients were under only topical treatments, 10 patients (3.6%) were under systemic antibiotic treatment with topical treatment, and 114 patients (41%) were under oral isotretinoin treatment. During this period, for 3 patients topical treatments were switched to oral isotretinoin because of severity of acne and 1 of the patients under doxycycline treatment was switched to isotretinoin due to lack of efficacy. The rate of total acne patients treated with isotretinoin during the pandemic period was 50% (139 patients). Of these patients, 114 (76%) were follow-up ones, 16 (5.8%) of them were started isotretinoin treatment in their first visits.

The number of patients with first admission was statistically higher in non-pandemic period and the number of follow-up patients was statistically higher in pandemic period (P < 0.05). There was no statistically significant difference in the two periods according to the number of treatment naïve patients, the first admission patients previously treated with any systemic agent, and patients to whom was given systemic treatment in first admission (P > 0.05). The rate of acne patients treated with isotretinoin during the pandemic period and non-pandemic period were 50% and 39.3%, respectively. Isotretinoin use was found significantly higher in the pandemic period (P = 0.003). There was no statistically significant difference between the pandemic period and the non-pandemic period in terms of starting isotretinoin treatment in patients with first admission (P > 0.05). There was no significant difference for using isotretinoin treatment in patients who were under follow-up in the two groups (P = 0.17).

Follow-up intervals, drop-out rates and reported adverse events in patients treated with isotretinoin during pandemic and non-pandemic period are given in Table 3. The rate of patients who used isotretinoin and dropped out from follow-up during the pandemic period was significantly higher than the control group (P < 0.001). During the pandemic period, the rate of patients using isotretinoin, which was followed in every two or more-months, was significantly higher than the control group (P < 0.001). Side effects in pandemic and non-pandemic period were seen in 10.1% and 19.8% of the patients, respectively. The rate of patients using isotretinoin who developed side effects was found significantly higher in the non-pandemic period compared to the pandemic period (P = 0.01).

In the 4-month pandemic period (March-July 2020), only two patients were diagnosed with SARS-Cov-2 infection. One of the patients (aged 27 years) was using isotretinoin and she only showed mild upper respiratory tract infection symptoms. Other patient (aged 39 years) was using topical treatments. Neither of them was hospitalized.

### Table 2. Treatment Status of Patients Admitted During the Pandemic and Non-Pandemic Period

<table>
<thead>
<tr>
<th>Patients with first admission</th>
<th>Pandemic period (n = 278)</th>
<th>Non-Pandemic period (n = 577)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>124 (44.6%)</td>
<td>336 (58.2%)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Treated with any systemic agent (antibiotics and oral isotretinoin)</td>
<td>116 (93.5%)</td>
<td>318 (94.6%)</td>
<td>0.652</td>
</tr>
<tr>
<td>Treatment naive patients started systemic isotretinoin</td>
<td>39 (31.4%)</td>
<td>129 (38.3%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td>150 (54%)</td>
<td>239 (41.4%)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Isotretinoin treatment</td>
<td>114 (76%)</td>
<td>173 (72.4%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Systemic antibiotic treatment and topical treatments</td>
<td>10 (6.7%)</td>
<td>8 (3.3%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Only topical treatments</td>
<td>26 (17.3%)</td>
<td>58 (24.3%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Treatment status in all patients**

| Isotretinoin treatment       | 139 (50%)                | 227 (39.3%)                 | 0.003    |
| Systemic antibiotic and topicals | 36 (12.9%)              | 103 (17.9%)                 | 0.43     |
| Only topical treatment       | 103 (37.1%)              | 247 (42.8%)                 | 0.43     |
Table 3. Changes in Follow-Up Intervals, Patient Drop-Out Rates, and Reported Adverse Events in Isotretinoin Patients

<table>
<thead>
<tr>
<th>Number of isotretinoin patients</th>
<th>Pandemic period (n = 139)</th>
<th>Non-pandemic period (n = 227)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Followed-up for extended intervals</td>
<td>79 (56.8%)</td>
<td>65 (28.6%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>30 (21.6%)</td>
<td>6 (2.6%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Reported adverse events</td>
<td>14 (10.1%)</td>
<td>45 (19.8%)</td>
<td>0.01</td>
</tr>
<tr>
<td>liver enzyme abnormality</td>
<td>5 (3.6%)</td>
<td>10 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>hypertriglyceridemia</td>
<td>2 (1.4%)</td>
<td>6 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>back pain</td>
<td>2 (1.4%)</td>
<td>9 (4%)</td>
<td></td>
</tr>
<tr>
<td>nasal bleeding</td>
<td>2 (1.4%)</td>
<td>3 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>psychiatric symptoms</td>
<td>1 (0.8%)</td>
<td>3 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>headache</td>
<td>1 (0.8%)</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>severe xerosis-eczematous dermatitis</td>
<td>1 (0.8%)</td>
<td>4 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>dry eye syndrome</td>
<td>-</td>
<td>7 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>photosensitivity</td>
<td>-</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>anal fissure</td>
<td>-</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Novel coronavirus pandemic has caused significant changes in dermatology practices [3]. As depicted in our study, the accessibility to outpatient clinics and patient compliance with systemic treatments were affected by the pandemic. According to recent literature, acne patients consisted of the majority of the patients who are admitted to dermatology outpatient clinics [1], and treatment compliance was the highest in this group [3]. This might be due to that acne is relatively common condition in younger individuals and younger patients seek more care because of the psychosocial effect of the disease [4]. Additionally, the knowledge of the mild disease course of COVID-19 infection might cause young patients to reach hospital clinics without fear compared to elderly population [6]. Another reason for increased percentage of acne patients can be intense use of masks, thus causing increased prevalence of ‘mask acne’, likely result of increased usage of personal protective equipment with the current pandemic [6]. The percentage of acne patients admitted to dermatology outpatient clinic during the pandemic period was found significantly increased compared to non-pandemic period in the current study.

Starting from March 2020, social distancing measures and restrictions were imposed to prevent the spread of the virus by Turkish Authorities, however, hospital admissions were exempted. These restrictions were thought to not affect the admissions of acne patients. While the rate of acne patients admitted for their first visit was significantly low in pandemic period, the rate of patients who were admitted for follow-up visits was significantly higher. This is probably as a result of avoidance of hospital visits due to non-emergent conditions during the pandemic period and high treatment compliance rate of our patient population.

Theoretically, isotretinoin treatment may cause disruption of the basement membrane of the mucosal surfaces by causing mucosal dryness and thinning. This, hypothetically, can increase the risk of COVID-19 transmission [9]. There is no established guideline regarding the use of isotretinoin during the pandemic period. In the beginning of the pandemic British Association of Dermatologists recommended starting or continuing oral isotretinoin treatment where the risks are outweighed by the benefits with monthly follow-up [10]. According to this statement, if there is no risk of pregnancy, the prescriptions for several months could be given taking into account the need to monitor blood test and side effects with remote consultations. In situations where it is not possible to perform monthly pregnancy tests, home pregnancy tests are recommended as a suitable alternative [11]. With the rapid growth of teledermatology, these recommendations have been practiced and the patients were able get their prescriptions instead of in-person visits [2]. A recent study by Ruggiero et al reported high degree of satisfaction and well-being after teledermatology visits [12].

Between the pandemic and non-pandemic periods, there was no significant difference in the rate of starting systemic treatment for acne patients who were admitted for their first visit. Additionally, the percentage of patients using isotretinoin during pandemic period was significantly higher compared to non-pandemic period. This was due to a relative increase of the number of patients who were followed-up with their current isotretinoin treatment. In our clinic, isotretinoin therapy was not avoided during the pandemic period.

Isotretinoin treatment needs to be monitored in terms of both teratogenesis and bone marrow and metabolic side effects (leukopenia, hypertriglyceridemia, liver enzyme abnormalities) [14,15]). Although there are many studies that
do not support monthly laboratory testing for isotretinoin [15], there are many centers that apply monthly laboratory follow-up in clinical practice, especially in terms of teratogenicity [16]. Monthly laboratory monitoring is also a common practice among physicians in our clinic. When we compared the monthly follow-up to in every two or more-month follow-up rate between the 2 groups, in every 2 or more-month follow-up the rate was higher during the pandemic period. Our retrospective analysis showed that extended follow-up intervals showed no significant difference for detecting side effects of isotretinoin. Additionally, the reported side effect rate was significantly lower during the pandemic period. This might be due to the lock-down and increased use of skin care products due to easy accessibility to emollients and other protective measures.

In the 4-month follow-up, only one patient under isotretinoin treatment had a positive SARS-Cov-2 PCR result and she showed only mild upper respiratory tract infection symptoms. Thus, isotretinoin treatment seems efficacious and safe during pandemic. We recommend extended intermittent laboratory follow-up to reduce the risk of SARS-Cov-2 transmission, however further large cohort studies are required to elaborate the risks.

Acne patients constitutes an important part of dermatology outpatient clinics. The proportion of acne patients was observed as significantly higher during the pandemic period. This most likely reflects young individuals seek for more care due to psychosocial effects of the disease and less fear of infection by SARS-Cov-2. Another reason for increased percentage of acne patients is intense use of masks, causing increased prevalence of ‘mask acne’, likely result of increased usage of personal protective equipment with the current pandemic. During pandemic period, the majority of acne patients was admitted for follow-up and physicians did not avoid using isotretinoin treatment in the follow-up patients. Extended follow-up periods were adopted by physicians and were found safe and effective in the current study. Thus, isotretinoin treatment seems efficacious and safe during pandemic.

References


“Mole removal” on Instagram Hashtags: A Cross-sectional Analysis: Nevus Treatment Methods on Instagram

Semih Güder¹, Hüsna Güder²

1 Department of Dermatology, Medical Faculty, Bezmialem Vakif University, Fatih, Istanbul, Turkey
2 Department of Dermatology, Medical Faculty, Maltepe University, Maltepe, Istanbul, Turkey

Key words: Instagram, nevus treatment, plasma energy devices, cauterization, social media, non-physicians practice


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Competing interests: None.

Authorship: Both authors have contributed significantly to this publication.

Corresponding author: Semih Güder, Department of Dermatology, Medical Faculty, Bezmialem Vakif University, Fatih, Istanbul, Turkey. E-mail: semihguder@gmail.com

ABSTRACT

Introduction: With the increase in the use of social media, there is a steady increase in demand for medical, surgical, and cosmetic procedures. Dermatologists and other physicians are leaving their cosmetic practice to non-physician service providers to keep up with the growing demand for cosmetic procedures.

Objectives: To examine the gender, professions, and the method of nevi treatment of the profiles using #bensilme and #moleremoval hashtags on Instagram and to investigate the extent of cosmetic procedures comparing Turkey’s situation with other countries.

Methods: In Instagram, the most frequently used hashtags about nevus treatment were scanned by two dermatologists. We recorded profession, gender, country of origin, and the treatment method of nevi of profiles sharing the related posts.

Results: The countries with the highest share of the #moleremoval hashtag were the United Kingdom (15%), India (12%), and the United States of America (10.5%), and the proportion of physicians in these countries was 16.7%, 100%, and 71.4%, respectively. In the non-physician group, plasma pen method in our country is the most used method (Turkey: 97.9%, world: 75% respectively), but the use of radiofrequency cautery (world: 12.5%, Turkey: 1% respectively) and cryo pen (world: 7.5%, Turkey: 0.0%) methods were significantly more abroad.

Conclusions: We demonstrated that non-physicians mostly perform nevus destruction procedures. Physicians must use social media more actively to share educational, quality, and accurate information. We suggest that the hashtags used by physicians in their social media posts should be chosen from the words used in the folk language.
Introduction

Instagram is a free social networking service for sharing photos and videos [1]. The number of daily users reached 500 million on the platform, which reached 1 billion active users per month in the last month of 2018 [2,3]. Hashtags are keywords those social media users utilize to tag their posts. They are used to organize the share content, search and collect data [4,5]. More than 40% of people in the United States use social media to get health information. Many people decide to receive healthcare services based on their social media posts [5].

With the increase in social media usage, there is a steady increase in demand for medical, surgical, and cosmetic procedures. This has increased in people applying to non-physicians for cosmetic procedures and aesthetic medical treatments. Dermatologists and other physicians leave cosmetic procedures to non-physician service providers to keep pace with the growing demand for cosmetic procedures. Non-physician groups (aestheticians, nurses, doctor assistants, nurse assistants, make-up experts, hairdressers, etc.) harass the specialty of medical science. This situation is directly related to patient health and safety. In addition, patients treated by non-physicians experience more burns and pigmentation problems than patients treated by physicians [6]. This situation is beyond the development of blemishes and burns. Melanoma, which is evaluated and destroyed by non-physicians as a simple nevus, can shorten the patient’s life span and increase the treatment costs significantly [7].

While using Instagram, we observe non-physicians also do that nevus destruction in our searches related to nevus treatment. We anticipate that such practices performed in incompetent hands may endanger patient health and safety. Therefore, we aimed to evaluate the professions of the profile owners and methods by using the most two hashtags related to nevus treatment on Instagram.

Objectives

We want to examine the gender, professions, and the method of nevi treatment of the profiles using #bensilme and #moleremoval hashtags on Instagram and to investigate the extent of cosmetic procedures comparing Turkey’s situation with other countries. In particular, we wanted to investigate the rate of non-physician practices in this regard.

Methods

Study Design

On May 01, 2021, two dermatologists scanned the most frequently used hashtags for nevus treatment on Instagram. The most shared hashtags related to nevus treatment, were selected in Turkish and English One hundred posts using the #bensilme hashtag in Turkish and 100 posts using the #moleremoval hashtag, which may have an English equivalent, were planned to be examined. The analysis was started from current posts to old-dated posts, and especially melanocytic nevus-looking posts were examined. The compatibility of the shared images with melanocytic nevus was determined by the joint decision of the two dermatologists. We ended the study when we reached 100 posts from each hashtag. Information on profession, gender, country of origin were collected from the profiles that shared them. The profession information specified in the profiles that share related posts was taken as a basis for the distinction between physicians and non-physicians and for the determination of other professions. In order to determine the professions of the profile owners who did not have information of professions and gave their own website information in their profiles we reached their websites. If information of profession is specified in the “about us” section of the website, we have recorded it. The information on the nevus destruction method used by the practitioners was obtained from the related posts. In data entry, we classified dermatologists and plastic surgeons as physicians. We defined the other specialists as doctors. Approval for this study was obtained from the Ethics Committee of Maltepe University Faculty of Medicine (Approval number: 2021/900/69).

Inclusion and Exclusion criteria

Melanocytic nevi, which have photos or videos both before and after destruction, were selected from publicly accessible posts. The selected posts included gender, profession, and destruction method information in the practitioner’s profile and posts. Duplicate profiles and posts missing at least one of the above information were not included in the study.

Statistical Analysis

We used the Shapiro-Francia test to evaluate the compatibility of univariate data to normal distribution. According to quantitative data, the Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups with each other. Pearson Chi-Square, Fisher Exact, and Fisher-Freeman-Holton tests were tested with the Monte Carlo Simulation technique to compare categorical variables. In addition, column proportions were compared and expressed according to Benjamini-Hochberg corrected P value results. Quantitative variables were represented in the tables as mean (± standard deviation) and median (25° and 75° percentile). Categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level, and a P value of less than 0.05 was considered significant. SPSS 27.0 (IBM Corporation) program was used to analyze variables.
Results

There were 21,711 posts in the #bensilme hashtag and 47,085 posts in the #moleremoval hashtag. The countries with the highest share of the #moleremoval hashtag in the world were the United Kingdom (15%), India (12%), and the United States of America (10.5%) (Table 1).

In our country, 21% of practitioners were male, and 79% were female. Abroad, this rate was similar to our country (30% and 70% respectively). We compared physician and non-physician groups in terms of gender. The number of male physicians in the world was significantly higher than in our country (respectively 93.3%-19.0%, P <0.001). There was no physician among female practitioners in our country.

Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
<td>25.5%</td>
</tr>
<tr>
<td>Female</td>
<td>149</td>
<td>74.5%</td>
</tr>
<tr>
<td><strong>Profession</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esthetician</td>
<td>108</td>
<td>54.0%</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>28</td>
<td>14.0%</td>
</tr>
<tr>
<td>Doctor</td>
<td>21</td>
<td>10.5%</td>
</tr>
<tr>
<td>Hairdresser</td>
<td>18</td>
<td>9.0%</td>
</tr>
<tr>
<td>Plastic Surgeon</td>
<td>15</td>
<td>7.5%</td>
</tr>
<tr>
<td>Nurse</td>
<td>5</td>
<td>2.5%</td>
</tr>
<tr>
<td>Masseur</td>
<td>4</td>
<td>2.0%</td>
</tr>
<tr>
<td>Make-up artist</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Physician / Non-physician</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>64</td>
<td>32.0%</td>
</tr>
<tr>
<td>Non-physician</td>
<td>136</td>
<td>68.0%</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmapen</td>
<td>136</td>
<td>68.0%</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>23</td>
<td>11.5%</td>
</tr>
<tr>
<td>Radiofrequency cautery</td>
<td>18</td>
<td>9.0%</td>
</tr>
<tr>
<td>Laser</td>
<td>16</td>
<td>8.0%</td>
</tr>
<tr>
<td>Electrocautery</td>
<td>4</td>
<td>2.0%</td>
</tr>
<tr>
<td>Cryopen</td>
<td>3</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>100</td>
<td>50.0%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>30</td>
<td>15.0%</td>
</tr>
<tr>
<td>India</td>
<td>24</td>
<td>12.0%</td>
</tr>
<tr>
<td>United States of America</td>
<td>21</td>
<td>10.5%</td>
</tr>
<tr>
<td>Australia</td>
<td>7</td>
<td>3.5%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>4</td>
<td>2.0%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>3</td>
<td>1.5%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2</td>
<td>1.0%</td>
</tr>
<tr>
<td>Venezuela</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Philippines</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Canada</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Nepal</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Russia</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Spain</td>
<td>1</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Table 1 continues
In the non-physician group, the proportion of men in our country was significantly higher than abroad (respectively 81.0%-6.7%, P < 0.001). In the non-physician group, the rate of women in our country was also significantly higher than abroad (100%-54.3%, respectively) (P < 0.001) (Table 2).

When physicians and non-physicians were compared, 96% of the practices in our country were performed by non-physicians and only 4% were performed by physicians (P < 0.001). Abroad, this rate was 60% and 40%, respectively (Table 2) (Figure 1). The countries that have the most shares of the #moleremoval hashtag abroad were UK, India, and the USA, and the proportion of physicians in these countries was 16.7%, 100%, and 71.4%, respectively (Table 3).

Considering the professions, the rate of estheticians and hairdressers in our country was significantly higher than abroad (81%-27% for estheticians, 14%-4% for hairdressers, respectively). Abroad, rate of doctors (18%-3% respectively), dermatologists (27%-1% respectively), plastic surgeons (15%-0.0% respectively), masseurs (4%-0.0% respectively) and nurses (5%-0.0% respectively) were significantly higher than our country (P < 0.001) (Table 2), (Figure 2).

In terms of the method of destruction, plasma pen was significantly higher in our country compared to abroad (96% - 40%, respectively). Abroad, rate of laser (14%-2%, respectively), surgical excisions (22%-1%, respectively), radiofrequency cauterizations (17%-1%, respectively), and electrocauterizations (4%-0%, respectively) were significantly higher than in our country (Table 2), (Figure 3).

The methods used by the physicians were similar in our country and abroad without significant difference (P = 0.577). In the non-physician group, plasma pen usage is more frequent in our country (Turkey: 97.9%, world: 75.0% respectively), but abroad radiofrequency cautery (World: 12.5%, Turkey: 1% respectively) and cryo pen (World: 7.5%, Turkey: 0.0% respectively) usage were significantly more (p<0.001) (Table 2).

### Discussion

We wanted to examine the Instagram accounts using #bensilme in Turkish and #moleremoval hashtags in English regarding gender, professions, and method of destroying nevus of profile owners. We planned this study to
Table 2. Statistical Analysis

<table>
<thead>
<tr>
<th></th>
<th>Turkey (n=100) n (%)</th>
<th>World (n=100) n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (21.0)</td>
<td>30 (30.0)</td>
<td>0.194</td>
</tr>
<tr>
<td>Female</td>
<td>79 (79.0)</td>
<td>70 (70.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Physician / Non-physician</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physician</td>
<td>4 (4.0)</td>
<td>60 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Non-physician</td>
<td>96 (96.0)</td>
<td>40 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physician</td>
<td>4 (19.0)</td>
<td>28 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Non-physician</td>
<td>17 (81.0)</td>
<td>2 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physician</td>
<td>0 (0.0)</td>
<td>32 (45.7)</td>
<td></td>
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<tr>
<td>Non-physician</td>
<td>79 (100.0)</td>
<td>38 (54.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Profession</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Esthetician</td>
<td>81 (81.0)</td>
<td>27 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Doctor</td>
<td>3 (3.0)</td>
<td>18 (18.0)</td>
<td></td>
</tr>
<tr>
<td>Dermatologist</td>
<td>1 (1.0)</td>
<td>27 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Plastic Surgeon</td>
<td>0 (0.0)</td>
<td>15 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Hairdresser</td>
<td>14 (14.0)</td>
<td>4 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Masseur</td>
<td>0 (0.0)</td>
<td>4 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td>0 (0.0)</td>
<td>5 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Make-up artist</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Methods used by physician's</strong></td>
<td></td>
<td></td>
<td>0.577</td>
</tr>
<tr>
<td>Plasmapen</td>
<td>2 (50.0)</td>
<td>10 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>1 (25.0)</td>
<td>13 (21.7)</td>
<td></td>
</tr>
<tr>
<td>Surgical excision</td>
<td>1 (25.0)</td>
<td>22 (36.7)</td>
<td></td>
</tr>
<tr>
<td>Electrocautery</td>
<td>0 (0.0)</td>
<td>3 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Radiofrequency cautery</td>
<td>0 (0.0)</td>
<td>12 (20.0)</td>
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<tr>
<td><strong>Methods used by non-physician's</strong></td>
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<td>&lt;0.001</td>
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<tr>
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<td>94 (97.9)</td>
<td>30 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>1 (1.0)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Electrocautery</td>
<td>0 (0.0)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Radiofrequency cautery</td>
<td>1 (1.0)</td>
<td>5 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Cryopen</td>
<td>0 (0.0)</td>
<td>3 (7.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Summary of methods</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasmapen</td>
<td>96 (96.0)</td>
<td>40 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Laser</td>
<td>2 (2.0)</td>
<td>14 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Surgical excision</td>
<td>1 (1.0)</td>
<td>22 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Electrocautery</td>
<td>0 (0.0)</td>
<td>4 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Radiofrequency cautery</td>
<td>1 (1.0)</td>
<td>17 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Cryopen</td>
<td>0 (0.0)</td>
<td>3 (3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Follower</strong></td>
<td>median (q1/q3)</td>
<td>median (q1/q3)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>3313 (1850.5 / 7021)</td>
<td>1372 (550 / 8197.5)</td>
<td></td>
</tr>
</tbody>
</table>

c=Pearson Chi-Square Test (Monte Carlo); ff=Fisher Freeman Halton test (Monte Carlo); u=Mann Whitney U Test (Monte Carlo); q1=percentile 25; q3=percentile 75. A=significance in the world population compared to Turkey, B=significance in the Turkish population compared to world.
Table 3. Distribution of Physicians and Non-Physicians in the World

<table>
<thead>
<tr>
<th></th>
<th>United Kingdom</th>
<th>India</th>
<th>United States of America</th>
<th>Other countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>5 (17)</td>
<td>24 (100)</td>
<td>15 (71)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Doctor</td>
<td>4 (13.4)</td>
<td>1 (4.2)</td>
<td>4 (19)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Dermatologist</td>
<td>1 (3.3)</td>
<td>18 (75)</td>
<td>4 (19)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Plastic Surgeon</td>
<td>0</td>
<td>5 (20.8)</td>
<td>7 (33.3)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Non-Physician</td>
<td>25 (83)</td>
<td>0</td>
<td>6 (29)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Esthetician</td>
<td>17 (56.6)</td>
<td>0</td>
<td>3 (14.3)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Hairdresser</td>
<td>4 (13.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Masseur</td>
<td>1 (3.3)</td>
<td>0</td>
<td>2 (9.6)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nurse</td>
<td>3 (10)</td>
<td>0</td>
<td>1 (4.8)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Figure 2. Distribution of physicians and non-physicians we have identified in Turkey and in the world. (numbers indicate percentages).

Figure 3. Distribution of destruction method we have identified in Turkey and in the world. (numbers indicate percentages).

Investigate the extent of non-physician practices and to compare the situation in our country with abroad. As a result of our research, we found that high rates of non-physician practices are performed in our country and overseas to treat nevi.

Nevus treatment options include total surgical excision, shave excision, lasers, radiofrequency, electrocautery, and cryotherapy. However, the possibility of recurrence is high after non-specific thermal or cold damage methods, and recurrent lesions are confused with atypical melanocytic nevi.
or melanoma. Due to the cosmetic appearance, it is necessary to eliminate the risk of dysplasia and melanoma in the nevus before starting nevus treatment. Thus, dermoscopy is a good tool in skilled hands, but it is still a more reliable method to biopsy in doubtful cases. In general, it is accepted that all nevi should be examined histologically as medicolegal. An average of 2.3% of melanocytic nevi considered to be clinically benign was reported as microscopic malignant [8-10]. While methods in which pathological examination cannot be performed are controversial for nevus treatment, it is unacceptable for non-physicians to treat nevus.

In terms of professions, the high number of estheticians and hairdressers in our country and in the UK may be because this group uses social media more actively or may prefer #bensilme and #moleremoval hashtags than physicians. On the other hand, the low rate of physicians in our country and the UK may be because physicians in these countries do not use social media actively, or it may also be since the doctor group in these countries use hashtags containing medical words instead of the more preferred hashtags in the spoken language.

We have seen that dermatologists produce a small portion of the #bensilme and #moleremoval hashtags posted on Instagram. However, in India, no one except the doctor used the #moleremoval disease. This may be since estheticians use more local languages than English, or India has provided this with its laws. There were only physician shares in Albania, Canada, Egypt, Iran, Nepal, and Pakistan, where 1 to 3 shares were examined, but no comment could be made because the number was low.

Plasma pen use was common in the non-physician group, especially in our country. This may be due to the fact that plasma pen devices are easily accessible, inexpensive, and practical to implement. However, it can also be caused by such devices not being recognized as medical devices. As a result of the application made by the Turkish Society of Dermatology Association to our Ministry of Health, the use of these devices in our country has been legally restricted to physicians only.

It is essential to get medical information on social media from reliable sources. Because people mainly apply to social media to make a treatment decision. Information from unqualified sources can lead to misdirection, unnecessary treatment, and potential harm. For this reason, it is crucial for dermatologists, plastic surgeons, and other physicians to share quality content [11]. Some studies in recent years show that Instagram is a very suitable platform for educating audiences around the world. It is even recommended that dermatologists be active on social media platforms in order to access evidence-based education resources. However, dermatology specialization programs still do not use social media actively enough [12-15].

Wong et al have compiled some suggestions for physicians on how create a professional Instagram account. These are as follows: must be an official account, the content must be short and precise, supported with images and videos, must be online frequently, stories and posts must be share regularly, a disclaimer must be prepared for followers with medical concerns, a good patient consent form should be prepared to share patient information [2].

Conclusions

We have demonstrated that non-physicians widely use nevus destruction procedures. However, wrong only disappears when the right turns out. Therefore, we think physicians must use social media more actively and share quality and accurate information. We suggest that physicians in Turkey use #bensilme and other related tags in their social media posts on this issue, which may fill the gap in this area. In addition, physicians must share quality information on social media for educational purposes that tissue destruction devices are medical devices and must be used by physicians.

Data Availability Statement: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Transparency Statement: The lead author (Semih Güder), affirms that this manuscript is an honest, accurate, and transparent account of the study being reported that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

Dermoscopy of Nevus Lipomatosus Cutaneous Superficialis in a patient with Skin Type IV

Boina Kinnera¹, Sreeramu Suggu¹, Venkatachalam Konakanchi¹

¹Department of DVL, Andhra medical college, Visakhapatnam, Andhra Pradesh, India

Key words: Dermoscopy, NLCS, cerebriform appearance, Indian skin

Citation: Kinnera B, Suggu S, Konakanchi V. Dermoscopy of nevus lipomatosus cutaneous superficialis in a patient with skin type IV. Dermatol Pract Concept. 2022;12(1):e2022001. DOI: https://doi.org/10.5826/dpc.1201a01

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Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding author: Dr. Konakanchi Venkatachalam, Department of DVL, Andhra medical college, Visakhapatnam, Andhra Pradesh, India. Email: drkvchelam99@gmail.com

Introduction

Nevus lipomatosus cutaneous superficialis (NLCS) is a hamartomatous condition characterized by the presence of mature lipocytes in the dermal tissue [1]. Very few case reports had been published on the dermoscopic appearance of NLCS. We, herein, describe the dermoscopic appearance of NLCS in the skin of an Indian man.

Case Presentation

A 32-year-old man with skin type IV presented with a 1-year history of a slowly growing painless swelling, which consisted of papules grouped into a papillomatous plaque over the left side of his lower back (Figure 1). Dermoscopie examination was done using a DermLite DL4 dermatoscope (×10) with polarized mode and pigment-enhancing mode. It showed a cerebriform pattern with sulci and gyri, multiple yellow-colored structureless areas, white structureless areas, meshwork-like pigmented lines, where a few lines were seen as 2 parallel lines, keratotic plugs in the sulci, and a rim of white homogenous area at the periphery (Figure 2A). The prominence of yellowish structures around hair follicles was not noted in this case, as has been described in literature on similar phototype. The pigment-enhancing mode on dermoscopy
showed enhancement of the yellow structureless areas (dermal lipocytes) and white structureless areas (dermal collagen) which further favors the diagnosis of NLCS (Figure 2B). The cerebriform surface seen on dermoscopy represents the uneven surface formed by sulci and gyri, the yellow structureless areas represent dermal adipocytes, the presence of a regular pigment indicates the relative histological preservation of the normal rete ridges [2], and the white structureless areas represent the perifollicular fibrosis and thickened collagen in the dermis. Our findings are consistent with the dermoscopic features described previously by Vinay et al who described 5 features of NLCS: cerebriform appearance, web-like regular pigment network, rim showing a white veil, yellowish structureless areas, and comedo-like openings [2]. The differentials include lymphangioma circumscriptum, nevus sebaceous and neurofibromatosis.

Conclusions

Dermoscopy serves as a non-invasive tool in the diagnosis of NLCS and helps to differentiate it from other cutaneous conditions like lymphangioma circumscriptum, nevus sebaceous and neurofibromatosis.

References

Crusted Umbilicated Papules in a Child

Hitashi Mehta1, Sheetanshu Kumar1, Divya Aggarwal2, Debajyoti Chatterjee2, Keshavamurthy Vinay1

1 Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
2 Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Key words: reactive perforating collagenosis, RPC, perforating disorders

Citation: Mehta H, Kumar S, Aggarwal D, Chatterjee D, Vinay K. Crusted umbilicated papules in a child. Dermatol Pract Concept. 2022;12(1):e2022002. DOI: https://doi.org/10.5826/dpc.1201a02

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Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding author: Keshavamurthy Vinay, MD, DNB, MNAMS, Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. E-mail: vinay.keshavmurthy@gmail.com.

Introduction

Reactive perforating collagenosis (RPC) is a rare benign perforating disorder characterized by transepidermal elimination of collagen fibers. Both familial and acquired forms of RPC exist, the latter in association with end-stage chronic kidney disease and diabetes mellitus. The very rare childhood form has slight male predilection and is commonly familial [1].

Case Presentation

Dermatology consultation was sought for a school-age child with multiple mildly itchy, red, raised lesions on his face and dorsum of hands, which were first noticed by the parents at 2 years of age. The parents also reported spontaneous healing of a few of the lesions with residual hypopigmented scars. Preceding history of insect bites or trauma was denied.

He was born out of a non-consanguineous marriage, and no one in family had a history of similar lesions. Examination revealed multiple skin-colored to erythematous discrete papules on both cheeks (Figure 1A) and dorsum of hands (Figure 1B) with central adherent keratotic plugs along with few well-circumscribed areas of atrophic scars. Dermoscopy of an individual lesion is presented in Figure 2A. Routine laboratory parameters including renal function tests, fasting blood sugar, and urinalysis were within normal limits. Histopathological examination of a facial papular lesion revealed compact ortho- and parakeratotic epidermis with a cup-shaped lesion lined by acanthotic epidermis on both sides along with mild perivascular and perianexial lymphomononuclear cell infiltrate mixed with collagen bundles in the dermis (Figure 2B). Altered collagen could be seen extruding trans epidermally through the cup-shaped depression. A diagnosis of RPC was reached. The child was treated with topical retinoind 0.025% ointment with satisfactory improvement after 1 month.

Conclusions

Familial RPC commonly presents as erythematous papules with central adherent scale-crust over the extensor aspect of
extremities. Superficial trauma precedes most lesions. Individual lesions heal within 6-10 weeks, but recurrences are common. Although the familial and acquired forms appear similar in morphology and on histopathology, the acquired form tends to be more persistent and shows transepidermal elimination of both collagen and elastin.

The central homogeneous yellowish area observed on dermoscopy corresponds to the central scale or crust, and the white rim of varying thickness corresponds to the epidermal invagination, along with an erythematous halo which arises due to small blood vessels around the lesion [2]. Histopathology reveals a plug of keratotic debris with vertically oriented collagen fibers extending into the plug, along with parakeratosis, epithelial hyperplasia, and dyskeratotic keratinocytes [1].

The diagnosis is mostly clinical and requires histopathology for confirmation. Investigations other than punch biopsy.
biopsy are neither necessary nor contributory. Differential diagnosis includes papular urticaria, prurigo nodularis, perforating folliculitis, and elastosis perforans serpiginosa.

Along with avoidance of trauma, topical therapies reported to be successful include retinoids, corticosteroids, and salicylic acid. Other therapies are systemic antihistamines, retinoids, methotrexate, photochemotherapy, NB-UVB, and cryotherapy. Most of the patients have a relapsing-remitting course throughout their lifetimes.

Childhood RPC is a rare entity with an obscure etiopathogenesis and usually self-limiting course. Awareness among clinicians regarding this entity is imperative in order to avoid misdiagnosis, anxiety among parents, and over-aggressive management.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.

References


Dermoscopic Features of Nevoid Hyperkeratosis of the Nipple and Areola

Conforti Claudio¹, Dri Arianna¹, Giuffrida Roberta², Zalaudek Iris¹, di Meo Nicola¹

¹ Dermatology Clinic, University of Trieste, Maggiore Hospital, Piazza dell’Ospitale 1, Trieste, Italy
² Experimental Dermatology Section, Division of Dermatology, University of Messina, Messina, Italy

Key words: nevoid hyperkeratosis of the nipple and areola, asymptomatic plaques, hyperpigmented plaque, hyperkeratosis

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Corresponding author: Claudio Conforti, MD, Dermatology Clinic, University of Trieste, Trieste, Italy. E-mail: claudioconforti@yahoo.com

Introduction

Nevoid hyperkeratosis of the nipple and areola (NHNA) is a rare benign condition characterized by verrucous, pigmented, and asymptomatic plaques involving the nipples and areolas. Only a few cases have been reported in literature since this entity was firstly described in 1923. The etiology is still unknown, but it is hypothesized that it occurs in correlation with hormonal changes because it is more frequent in women during childbearing age, and it worsens during pregnancy.

Case Presentation

We present the case of a 27-year-old Caucasian woman referred in for consultation to our skin cancer department with a 9-month history of a lesion involving the right nipple and the areola. Examination revealed a hyperpigmented plaque of about 35 mm in diameter and with well-defined borders (Figure 1B). The lesion was completely asymptomatic, and the patient denied pain, pruritus or discharge. She was otherwise healthy, and breast examination and general physical examination were negative. Hair, nails, and mucosal sites were normal. The patient was not on medication, and she was not pregnant.

Dermoscopic evaluation (×20, DermLite) showed the presence of a homogeneous brown network with some hyperkeratotic areas showing yellow-brown scales (Figure 2, A and B). These dermoscopic findings are in accordance with other previous cases of NHNA, and the diagnosis was later confirmed performing a biopsy.

Discussion and Conclusions

Cinotti et al reported that at dermoscopic examination the NHNA showed a papillomatous surface with pink homogenous areas, whitish desquamation, red dots, and erosions [1]. Mazzella et al reported a peculiar case of NHNA resembling a pigmented basal cell carcinoma with multiple blue-gray globules and leaf-like areas [2].
In the past, skin biopsy was certainly the most accurate way to make a diagnosis of NHNA, but it could create a scar in a delicate and intimate area. Histopathological examination of NHNA can show variable findings such as acanthosis, hyperkeratosis, papillomatosis, keratin plugging, perivascular infiltrates of CD41 lymphocytes, melanophages and plasma cells in the superficial dermis, and hyperpigmentation of the basal layer and dermal fibrosis [1]. Although the histopathological examination remains the gold standard for the diagnosis, sometimes the patient does not accept this option. Dermoscopy offers the possibility of making a correct diagnosis without resorting to incisional biopsy, even if standard dermoscopic diagnostic criteria have not been defined yet. The role of dermoscopy is certainly crucial for the differential diagnosis of areola and nipple lesions, which include seborrheic keratosis, acanthosis nigricans, Darier disease, epidermal nevus, basal cell carcinoma, Bowen disease, Paget disease, contact allergic dermatitis, chronic eczema, dermatophytosis, mycosis fungoides, and reticulate papillomatosis.

All the above pathologies can be diagnosed well with dermoscopy, and for this reason our case underlines the importance of a dermoscopic evaluation of hyperpigmented or non-pigmented lesions of the areola and nipple to reduce excision rate and increase diagnostic accuracy of special-site lesions.

Informed consent: Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

References


Diffuse Juvenile Bullous Pemphigoid Managed Successfully With a Short Course of Cyclophosphamide

Seema Rani1, Diksha Aggarwal1, Kabir Sardana1, Savitha Bathula1, Purnima Malhotra2

1 Department of Dermatology, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, New Delhi, India
2 Department of Pathology, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, New Delhi, India

Key words: immunobullous, bullous pemphigoid, cyclophosphamide, juvenile bullous pemphigoid

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Corresponding author: Seema Rani, Associate Professor, Department of Dermatology, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, New Delhi, India. E-mail: drseemashekhar@gmail.com

Introduction

Adolescent bullous pemphigoid (BP) is a very rare entity—with generalized (erythrodermic) variant being even rarer—and management of such difficult BP cases can be challenging.

Case Presentation

A 17-year-old girl presented with a 1-month history of intense pruritus that was followed by the development of multiple fluid-filled lesions. These lesions ruptured spontaneously in 3 to 4 days and left behind painful erosions. There was no history of drug intake, trauma, recent vaccination, fever, or photosensitivity. Notably, she had an intellectual disability; however, the psychiatric consultation was normal. Cutaneous examination revealed multiple tensevesicles, both clear and hemorrhagic, and bullae over an erythematous base that involved 90% of the body surface along with involvement of head and neck areas (Figure 1A). Nails and mucosa were unaffected. Bulla spread sign was positive and Nikolsky sign was negative. Tzanck smear showed eosinophils and neutrophils. The total leukocyte count was 20,000 per mm³ with 77% eosinophils in differential leukocyte count and an absolute eosinophil count of 15,400 per mm³. The serum immunoglobulin (Ig) E level was normal. Histopathology revealed focal clefting at the dermoepidermal junction and perivascular mononuclear inflammatory infiltrate with numerous eosinophils in the superficial dermis (Figure 1B). Direct immunofluorescence revealed linear deposits of IgG and C3 along the basement membrane zone. Based on clinical presentation and histopathological and immunological findings, a diagnosis of diffuse adolescent BP was made. The BP disease area index score was 145.
Oral prednisolone 70 mg along with broad-spectrum antibiotic cover and antihistamines were started. Doxycycline 100 mg and nicotinamide tablets 500 mg were added as steroid-sparing agents, but there was a progressive increase in the severity of the eruption. As a consequence, Doxycycline was replaced by azathioprine 50 mg twice daily. In spite of 4 weeks of azathioprine, there were 40-50 new blisters per day, and in view of the recalcitrance, azathioprine was discontinued and cyclophosphamide 100 mg was added. After 2 weeks, the number of new lesions gradually decreased and old lesions started to heal. The patient was discharged on prednisolone 50 mg and cyclophosphamide 100 mg. Two weeks later the dose of cyclophosphamide and prednisolone was tapered to 50 mg and 40 mg, respectively. During treatment patient routine hematological investigations and urinalysis were normal. Over the next 4 weeks, cyclophosphamide was stopped. Azathioprine was restarted at a dose of 25 mg and gradually increased. Currently the patient is undergoing oral prednisolone 15 mg and azathioprine 50 mg with a good control of her disease without any side-effects. The patient is on regular follow-up at a 4- to 6-week intervals with no relapse of bullous lesions but with residual pigmentary changes (Figure 2).

Informed consent has been taken from patient guardian (patient is minor) for the nature and side-effects of drug (cyclophosphamide).

Conclusions

BP is the commonest immunobullous disorder worldwide, but it is rare in childhood (100 cases) and extremely uncommon in adolescence (14 cases) [1]. Childhood BP is diagnosed according to the criteria of Nemeth, and our case satisfied these criteria. BP is generally more responsive to treatment than pemphigus vulgaris, but there are refractory cases in which treatment resistance occurs. Childhood BP usually has a good prognosis, although, in some cases the course is less benign [2]. Our case had generalized BP, poor response to high doses of steroid, anti-inflammatory, antibiotics and azathioprine. Non-availability of biologics at our center and economic constraints resulted in the use of cyclophosphamide that was administered as a “rescue therapy” in view of its side effect profile. Our case exemplified the role of cyclophosphamide as a short-term bridge therapy, after which the patient was adequately controlled on azathioprine. In a severe and recalcitrant case, such as this one, cyclophosphamide can be used to bring the disease under control.

Informed consent: Written informed consent for publication of clinical details and clinical images was obtained from the patient.

References


Dermatology Practical & Conceptual

Yellow Plugs: An Additional Dermoscopic Criterion in the Diagnosis of Primary Cutaneous B-Cell Lymphoma

Claudio Conforti¹, Roberta Giuffrida², Arianna Dri¹, Iris Zalaudek¹, Nicola Di Meo¹

Introduction

Primary cutaneous B-cell lymphoma (PCBCL) is a lymphoproliferative B-cell disorder involving only the skin at the time of diagnosis. PCBCLs comprise a group of rare disease that account for 20%-25% of all cutaneous lymphomas, and they are classified into 3 main types: (i) follicle center lymphoma (the most common and usually indolent), (ii) marginal zone lymphoma, and (iii) diffuse large B-cell lymphoma (the most aggressive) [1].

Case Presentation

We present the case of a 63-year-old otherwise healthy Caucasian woman who sought consultation at our skin cancer department for a cluster of lesions localized on the right cheek, presenting as pinkish-erythematous, slow-growing, firm nodules, irregularly oval in shape, with well-defined borders, that had been enlarging over the past 8 years. The largest nodule was 30 mm in diameter (Figure 1A). The patient denied correlation with traumas or arthropods bites and felt no local pain or itch. No other cutaneous lesions were found at total-body checkup. Systemic involvement was ruled out with laboratory tests, ultrasound examination of lymph node stations, and computed axial tomography of chest and abdomen.

Dermoscopic evaluation (×20; DermLite, 3Gen) showed the presence of an erythematous background with salmon-colored areas, arborizing vessels, and peculiar yellow plugs surrounded by well-defined white circles (Figure 1B). The integration of the clinical history and information provided by dermoscopy led to the hypothesis of B-cell lymphoma. A 5-mm punch biopsy was performed, and the histopathological report confirmed the clinical diagnosis of cutaneous B-cell lymphoma, follicle center subtype.
Conclusions

Overall, PCBCLs may clinically appear as papules, plaques, or nodules of different shapes, number, colors, and body locations. Differential diagnosis includes a wide spectrum of pathologies, such as basal cell carcinoma, amelanotic melanoma, arthropod bite scar, or keloid, and for this reason a skin biopsy is always needed to arrive at the correct diagnosis, even if dermoscopy can help rule out other skin disorders [2].

Currently available literature states that white circles and salmon-colored areas are the main common dermoscopic features of PCBCLs. Regarding vascularization, arborizing or serpentine vessels could be found, sometimes simultaneously, resulting in a polymorphous vascular pattern. Scales are a further criterion highlighted in a retrospective study [3-5].

Figure 1. (A) Clinical image of the follicle center of PCBCL: pinkish-erythematous firm nodules, irregularly oval in shape, with well-defined borders, located on the cheek. (B) Dermoscopy of the follicle center of PCBCL: erythematous background, salmon-colored areas, arborizing vessels, and yellow plugs surrounded by well-defined white circles.

Figure 2. (A) Tissue fragment of PCBCL obtained by punch biopsy (standard H&E, magnification ×10). (B) Histopathological picture of the lymphoma: nodular lymphoid infiltrates arranged in a follicular pattern in the dermis (standard H&E, magnification ×20).
The presence of yellow plugs dermoscopic examination of PCBCLs have yet to be reported.

In our patient, yellow plugs were detectable throughout the entire lesion, and particularly evident in the central area. The term “yellow plugs” refers to yellow structures surrounded by white circles combined with an erythematous background with salmon-colored areas and arborizing vessels. The histopathological examination described nodular lymphoid infiltrates arranged in a follicular pattern in the dermis. The follicles were atypical because of the absence of polarization and mantle and showed a reduction in the number of macrophages (Figure 2, A and B). The cell immunophenotypic patterns were CD20+, Bcl-6+, CD10+ and partial Bcl-2+. There was no evidence of adnexal involvement, so it can be assumed that the accentuated follicular plugging was the result of the upward displacement of the epidermis by the underlying conspicuous dermal infiltrate.

Although dermoscopy cannot replace the histopathological examination, the combination of an erythematous background, salmon-colored areas, white circles, arborizing vessels and/or scales, as previously reported by other authors, as well as peculiar yellow plugs, may be helpful in considering PCBCLs in the differential diagnosis of cutaneous pink nodules. The peculiar features listed can help in promptly suspecting a possible lymphoma and in identifying the correct site for biopsy. Moreover, dermoscopy can be used to monitor recurrences. Since PCBCLs comprise a group of rare diseases, further investigations are needed to deepen the knowledge on the subject.

Informed consent: Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

References

A Newborn with a Blasckoid-like Distribution Rash: Never Forget to Use the Dermoscope

Federica Filippi¹, Marco Adriano Chessa¹, Federico Bardazzi¹, Iria Neri¹

¹ Dermatology Unit, IRCSS Policlinico di S. Orsola, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

Case Presentation

A 30-day-old newborn presented with a 7-day history of an erythematous-crusted rash with a blasckoid-like distribution on his arm and lower limb (Figure 1, A and B). The baby was sleeping well, and systemic symptoms were absent. A complete blood exam showed no abnormalities except for a mild eosinophilia. Dermoscopy revealed crusted scabies (Figure 1C). The patient was treated with permethrin 5% cream, applied and left on the skin for 4 hours for 2 consecutive nights and then again for 2 consecutive nights after 7 days. Other family members were given the same treatment regimen, permethrin 5% cream, applied and left on the skin for 8 hours.

Teaching Point

Norwegian or crusted scabies is a variant of scabies with a massive infestation of Sarcoptes scabiei. Most cases are reported in immunocompromised patients; however, in an immature immune system, overcrowded living conditions can lead to the appearance of the disease in newborns. Our case is peculiar because of the absence of symptoms and the papulo-erythematous blasckoid-like presentation [1]. In these cases, dermoscopy has a central role in quickly arriving at a diagnosis and avoiding unnecessary investigation [2].

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Corresponding author: Marco Adriano Chessa, MD, Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy. E-mail: marco.adriano.chessa@gmail.com
References


Dermoscopy of Dermatomyositis in Dark Skin

Shekhar Neema¹, Rohit Kothari¹, Ahmed Waheed Kashif¹, Deepak Vashisht¹, Biju Vasudevan¹

1 Armed Forces Medical College, Pune, India

Key words: dermatomyositis, dermoscopy, dermatoscopy


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Corresponding author: Shekhar Neema MD, FEBDV, Associate Professor, Armed Forces Medical College, Pune, India.
E-mail: shekharadvait@gmail.com

Introduction

Dermatomyositis is an idiopathic inflammatory myopathy characterized by muscle weakness and cutaneous features such as heliotrope rash, Gottron papule, confluent macular erythema, poikiloderma, mechanic’s hand, ragged cuticle and periungal telangiectasia [1]. The characteristic cutaneous manifestations are difficult to appreciate in individuals with darker skin types thus making the diagnosis challenging.

Case Presentation

A 59-year-old woman presented with complaints of pruritic dark lesions over her entire body and progressive muscle weakness of 2 months’ duration. Examination revealed hyperpigmentation involving the face, periorcular region (heliotrope rash), upper back (Shawl sign), and V area of neck (V sign), hyperpigmented papules over the knuckles (Gottron papule), hyperpigmented macules on the hand (Gottron sign), hyperpigmented papules over the lateral aspect of the index finger and medial aspect of thumb (mechanic’s hand), and ragged cuticles (Figure 1, A-D).

Dermoscopy of the peri-ocular area revealed a brown reticular pigment network, gray dots and globules and linear out-of-focus vessels (Figure 1E). Dermoscopy of the Gottron papule shows white-to-pink structureless areas and a reticular pigment network (Figure 1F). Histopathology revealed atrophic epidermis, basal cell vacuolation, melanophages in the papillary dermis, and presence of focal mucin (Figure 1G). Creatinine phosphokinase was 573 IU/ml, antinuclear antibody was 3+ (speckled pattern). Magnetic resonance imaging of the thigh showed myositis, and high-resolution computed tomography of chest were suggestive of interstitial lung disease. A diagnosis of dermatomyositis was made based on clinical, histopathological, serological, and imaging findings. The patient was treated with methylprednisolone pulse of 1 g per day for 3 days, hydroxychloroquine 200 mg once a day and a tapering dose of oral steroids.

In a second case, a 45-year-old woman presented with similar complaints of photosensitivity, pruritic dark lesions over photo-exposed areas of the face, trunk, and extremities, swelling around the eyes, and proximal muscle weakness. Dermatological examination showed hyperpigmented macules over the forehead and lateral sides of cheeks and...
Figure 1. (A) Diffuse hyperpigmentation of face including peri-ocular (heliotrope rash), zygomatic, and nasolabial folds. (B) Hyperpigmented plaque over upper back (Shawl sign). (C) Hyperpigmented papules and macules over the knuckles (Gottron papule and Gottron sign). (D) Hyperpigmented papules over radial aspect of index finger (mechanic’s hand). (E) Dermoscopy of heliotrope rash shows brown reticular network, gray dots and globules (blue arrows) and linear out-of-focus vessels (blue stars) (DermLite DL4, polarized, x10). (F) Dermoscopy of Gottron papule shows white-to-pink structureless areas (blue arrows) and a reticular pigment network (blue star) (DermLite DL4, polarized, x10). (G) Histopathological examination shows an atrophic epidermis, basal cell vacuolation, melanophages, perivascular lymphocytic infiltrate and the presence of focal mucin (hematoxylin and eosin, x200). PAS stain shows the presence of mucin (inset).
erythema and edema involving the malar area (Figure 2, A and B). Dermoscopy showed a reticular pigment network, brown-to-gray dots and globules, and linear vessels (Figure 2D). The imaging, biochemical investigations, histopathology, and serology was consistent with diagnosis of dermatomyositis.

Conclusion

Cutaneous features are essential and characteristic in the diagnosis of dermatomyositis. Dermoscopy of Gottron papule has been described as a lump of surface scales and dotted vessels [2]. Individuals with darker skin present with predominant hyperpigmentation, that poses a diagnostic difficulty. Pigment incontinence that is seen in histopathology is due to basal cell damage and is seen as dots and globules on dermoscopy. Linear out-of-focus vessels are due to epidermal atrophy, and focal mucin deposition is seen as structureless white areas on dermoscopy. A reticular pattern on dermoscopy occurs due to melanization of the basal layer.

Dermoscopy may be helpful in the diagnosis of cutaneous features of dermatomyositis in darker skin. We also tried to correlate dermoscopic findings with histopathology. This is the first report on dermoscopy of dermatomyositis in darker skin to the best of our knowledge.

Informed consent: Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

References


Figure 2. (A) Hyperpigmented macules over the forehead and erythema and edema over the malar area. (B) Hyperpigmented macules over the lateral aspect of the cheek. (C) Dermoscopy shows brown reticular network (orange arrow), gray dots and globules (blue arrow), and out-of-focus linear vessels (blue star) (DermLite DL4, polarized, x10).
Penile Exogenous Pigmentation Mimicking Melanoma

Sabina Vaccari1, Michelangelo La Placa1, Alessia Barisani1, Rossella Lacava1, Cosimo Misciali1, Giulio Tosti2, Valeria Gaspari1

1 Dermatology – IRCCS Policlinico di Sant’Orsola, Department of Experimental, Diagnostic and Specialty Medicine (DIMES) – Alma Mater Studiorum University of Bologna, Italy
2 Division of Melanoma Surgery, Sarcoma and Rare Tumors, IRCCS, Istituto Europeo di Oncologia, Milan, Italy

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Corresponding author: Alessia Barisani, MD, Dermatology – IRCCS Policlinico di Sant’Orsola, Department of Experimental, Diagnostic and Specialty Medicine (DIMES) – Alma Mater Studiorum University of Bologna, Italy. Email: alessiabarisani@gmail.com

Introduction

The diagnosis of mucosal pigmented lesions can be challenging, as several differential diagnoses, including benign nevi, melanosis, melanoma, as well as post-inflammatory and physiological pigmentations, should be acknowledged. We report a case of penile exogenous pigmentation clinically and dermoscopically mimicking a malignant melanoma.

Case Presentation

A 65-year-old Caucasian man was referred to our attention because of an asymptomatic flat pigmented lesion of the penis. He reported that the lesion had appeared about 6 months earlier. Four years before, he had been diagnosed with genital lichen sclerosus and had undergone circumcision. Clinical examination revealed a brown pigmented asymmetrical flat lesion with irregular borders on the glans and the adjacent shaft (Figure 1A).

Videodermoscopy (FotoFinder dermatoscope, Fotofinder Systems, GmbH) showed a multicomponent pattern with an uneven pigmentation, multiple irregular brown-to-black dots, a blue-whitish veil and polymorphous vessels with some linear vessels at the periphery (Figure 1, B and C).

The main diagnostic suspicion was penile melanoma, due to the clinical and dermoscopic aspect and the patient's age; therefore, a skin biopsy was performed for confirmation. Histopathological examination revealed epithelium hyperplasia, sclerosis and brownish-black pigment in the superficial chorion, with no evidence of atypical melanocytic proliferation, suggestive of exogenous pigment (Figure 2, A and B). Immunohistochemistry was negative for S-100 and MART1, excluding a melanocytic neoplasm.

On the basis of the histopathological findings, a diagnosis of penile exogenous pigmentation in association with lichen sclerosus was made. We hypothesize that the lesion was a self-induced tattoo, even though the patient, suffering from a psychiatric disorder, did not confirm this hypothesis.
Figure 1. Penile exogenous pigmentation in a 65-year-old Caucasian man. (A) Clinical presentation of the lesion reveals a brown asymmetrical flat lesion with irregular borders. (B) Videodermoscopy shows a multicomponent pattern with uneven pigmentation, multiple irregular brown-to-black dots, a blue-whitish veil and polymorphous vessels, circle, original magnification ×20. (C) Arrow, original magnification ×60.

Figure 2. Penile exogenous pigmentation: histopathological findings consisting of epithelium hyperplasia, sclerosis and brownish-black pigment in the superficial chorion, with no evidence of atypical melanocytic proliferation. (A) Hematoxylin and eosin stain original magnification ×17. (B) Hematoxylin and eosin stain original magnification ×32.
On the basis of the histopathological findings, a diagnosis of a penile exogenous pigmentation in association with lichen sclerosus was made.

Conclusions

Penile melanoma is a rare entity, and therefore, its dermoscopic features have been described rarely. It may show a multicompartment pattern, multiple colors (brown, black, white, blue, red), a blue-whitish veil, regression structures, and some peripheral streaks [1]. The blue, gray, and white colors and the presence of structureless areas are considered strongly suggestive of mucosal melanoma. Although videodermoscopy is a useful tool for the early diagnosis of mucosal melanoma because different colors are more easily detectable in the mucosa than in the skin, in this case it did not prove useful for the diagnosis of a mucosal exogenous pigmentation, which may show the same dermoscopic features.

The homogeneous pattern shown on dermoscopy of skin tattoos has been described rarely [2]. The peculiar dermoscopic appearance of the lesion in our patient may be due to its localization on the mucosa; and as in melanoma, dermoscopy allows a better recognition of the colors and the vascular patterns. Moreover, the associated lichen sclerosus may have altered the dermoscopic features of the lesion. Mucosal hyperpigmentation often requires the exclusion of malignant melanoma by performing histopathological examination, especially when, as in this case, the clinical history is not helpful and diagnosis is often not possible on the basis of the clinical and dermoscopic examination alone.

Informed consent: Written informed consent for publication of his clinical details and clinical images was obtained from the patient.

References

Dermatofibrosarcoma Protuberans in the Palm of a 3-Year-Old Child

Omer Faruk Kumbuloglu¹, Fatih Barishan², Fevziye Kabukcuoglu³, Haci Mustafa Ozdemir²

¹ Department of Orthopaedics and Traumatology, Hand Surgery Division, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
² Department of Orthopaedics and Traumatology, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
³ Department of Pathology, Istanbul Sisli Hamidiye Etfal Application and Research Center, University of Health Sciences, Istanbul, Turkey

Key words: pediatric dermatofibrosarcoma protuberans, handpalm masses, Mohs micorgraphic surgery, imatinib

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Corresponding author: Fatih Barishan, MD, Department of Orthopaedics and Traumatology, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey. E-mail: drbarishan@hotmail.com

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a low-grade, locally invasive tumor that originates from cutaneous tissues. DFSP is the second most frequent skin sarcoma and is generally diagnosed between the ages of 30 and 50. It is mostly localized in the trunk, proximal extremities, or in the head and neck region [1]. There are a few reports showing DFSP in the dorsum of the hand of pediatric cases [2]. In this study, a case is presented of a 3-year-old boy that underwent 3 operations for DFSP in the palm of the hand.

Case Presentation

A 3-year-old male child presented to our clinic with a mass lesion at the level of the second metacarpophalangeal joint in the palm of the right hand. Two months before, the patient underwent surgical excision on the palm of his right hand at another clinic. The histological diagnosis was reported as lipofibromatosis at that time. Physical examination revealed a 1.5 cm × 2 cm mass in the same region (Figure 1A).

In the second surgical excision of the patient, the mass lesion was excised together with the overlying skin. The defective area that occurred at the excision site was closed with a full-thickness skin graft obtained from the right inguinal area. The histological examination showed a spindle cell lesion that started just below the epidermis and reaching the dermis and subcutaneous fat tissue, with short bundles crossing each other and continued beyond the surgical border. Marked atypia or mitotic activity was not observed. Immunohistochemical studies revealed widespread CD34 staining. The focal staining properties were observed using caldesmon and Alpha Smooth Muscle Actin stains. Desmin stain, HMB45, pancytokeratin, CD31, and calponin were all negative. The
Ki67 proliferation index was approximately 2-5% and the lesion was diagnosed as DFSP (Figure 1, B and C).

The patient was reevaluated following the histological diagnosis of DFSP and a subsequent chest X-ray did not show metastasis. Physical examination did not show any sign of lymphadenopathy. The third surgical excision was planned for the patient.

In the third surgical excision Mohs micrographic surgery was used. The surgical excision site was mapped with the tumor in the middle (Figure 2, A and B). The whole epidermal tissue, dermal tissue, first lumbrical muscle, and common palmar digital nerve were excised together with a tissue margin of 1 cm (Figure 2C). Since intraoperative frozen examination was reported as negative for the surgical border, a 4 cm × 3 cm wound site was left open and covered with surgical dressing, and a plaster was applied. The wound healed with a secondary closure in 6 weeks. There was no need for radiotherapy or imatinib treatment. There was no sign of recurrence at the end of the first postoperative year (Figure 2, D-F).

Conclusions

A diagnosis of DFSP is made upon clinical examination and histological evaluation of the patient and is often difficult due the frequently asymptomatic and slow progression. Histological diagnosis cannot be made with routine staining. Clinicians should consider DFSP in the differential diagnosis for pediatric palmar cutaneous masses; otherwise, a delay in diagnosis may cause a loss of hand function.

Informed consent: Written informed consent for publication of clinical details and clinical images was obtained from the patient.
Figure 2. (A) Appearance of the hand before Mohs micrographic surgery. (B) Tumor mapping, placing the lesion in the center. (C) After Mohs micrographic surgery. (D) Wound healing process following Mohs micrographic surgery 4 weeks postoperatively. (E, F) Appearance of the hand following Mohs micrographic surgery 1 year postoperatively with good function and no contracture development.
References


Large Congenital Melanocytic Nevus With Halo Phenomenon

Filiz Cebeci¹, Hasan Aksoy¹, Zeynep Arslan¹, Bengü Çobanoğlu Şimşek²

¹ Department of Dermatology, Istanbul Medeniyet University, Goztepe Suleyman Yalcin City Hospital, Istanbul, Turkey
² Department of Pathology, Istanbul Medeniyet University, Goztepe Suleyman Yalcin City Hospital, Istanbul, Turkey

Key words: Congenital melanocytic nevus, Halo phenomenon

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Corresponding author: Filiz Cebeci Assoc. Prof, Department of Dermatology, Istanbul Medeniyet University, Goztepe Suleyman Yalcin City Hospital, Istanbul, Turkey. Email: E-mail:cebecifiliz@yahoo.com

Introduction

Congenital melanocytic nevus (CMN) is a pigmented lesion present at birth or appearing in the first few weeks of life, with an incidence of 0.6%-1.6% among newborns. It develops from neural crest-derived melanocytes and usually enlarges throughout childhood. A CMN may remain unchanged or present a dynamic course [1,2]. Halo nevus or leukoderma acquisitum centrifugum can be defined by the presence of circular depigmentation around an acquired or congenital nevus; a halo can also develop around a melanoma. Herein, we report a male adolescent with halo phenomenon around a large CMN, an uncommon finding.

Case Presentation

A 14-year-old boy was admitted to our department due to complaint of enlargement and color change of a nevus on his right shin. The lesion had been present since birth and has grown over the years; during the past year, whitening of the skin was noted to develop around it. On physical examination, there was a 12 cm × 5.5 cm ellipsoid pigmented patch containing irregularly mottled hypopigmentation and few depigmented terminal hairs, surrounded by a 0.5-cm wide depigmented halo-like patch (Figure 1A). Dermoscopy showed regular network and globules, suggesting that the pigmented patch was melanocytic in origin (Figure 1B). The lesion was biopsied and histopathology revealed hypermelanosis at the basal cell layer, nests of nevomelanocytes in the dermis and periadnexial lymphocytic infiltration; in the areas corresponding to the depigmented part of the lesion, epidermal melanin and dermal nevus cells were notably absent (Figure 2, A-D). Based on the clinical and histopathological findings, the diagnosis was a large CMN with a halo phenomenon.

Conclusions

A halo phenomenon around a nevus has been suggested to be due to immunologic responses against melanocytes mediated...
Figure 1. (A) Melanocytic patch with irregularly mottled hypopigmentation, depigmented terminal hairs, and a depigmented halo. (B) Regular network, a few pigmented globules, and depigmented areas on dermoscopy.

Figure 2. Histopathology of the lesion. (A) Intradermal nevoid nests consistent with congenital melanocytic nevus. (B) Hypermelanosis in the epidermal basal cell layer corresponding to the hyperpigmented area. (C) Loss of epidermal melanin and dermal nevomelanocytes corresponding to the depigmented part of the lesion (H&E, ×200). (D) Loss of melanin in the basal cell layer (Masson-Fontana, ×400).
by cytotoxic T-cells or immunoglobulin M autoantibodies [2]. Unlike acquired nevi, the development of halo around a large congenital nevus is less common. Halo around CMN may also be accompanied by vitiligo. A CMN with a halo may eventuate in partial or complete regression of the pigmented lesion with progressive depigmentation, remain stable, or undergo repigmentation. Spontaneous involution of a CMN is uncommon [1,2]. Halo phenomenon around a CMN usually causes anxiety and may result in unnecessary surgical procedures. However, it is usually a benign condition and CMN patients with halo phenomenon should be followed up periodically, just as those with CMN without a halo phenomenon. It is suggested that a conservative approach and dermoscopic follow-up are safe for children with a CMN. Development of depigmentation around or within the CMN may be confused with pigmentary regression and conversion to malignant melanoma, and thus it is important to be aware of this phenomenon to avoid premature surgery, especially in children.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.

References


Dermoscopy of Lupus Miliaris Disseminatus Faciei Lesions in Different Stages of Evolution

Pankhuri Dudani¹, Nikhil Mehta¹

¹Department of Dermatology and Venereology, All India Institute of Medical Sciences, Delhi, India

Key words: dermatoscopy, lupus miliaris disseminatus faciei, telangiectasia, in-focus vessels, varioliform scar

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Corresponding author: Nikhil Mehta, MD, Department of Dermatology and Venereology. All India Institute of Medical Sciences, Delhi, India. E-mail: nikhilmehtadermatology@gmail.com

Introduction

Lupus miliaris disseminatus faciei (LMDF) is an uncommon chronic granulomatous disease of the head and neck region. Its dermoscopic features have recently been described, mainly in Fitzpatrick skin-types 2 and 3. Its etiology is unknown, and adults between the second and fourth decades of life are affected most.

Case Presentation

A 35-year-old man, Fitzpatrick skin-type 4, presented with asymptomatic yellowish-to-red-colored papules over the forehead, eyelids, nose, and ear helices; and elongated plaques over the neck, for 5 months. Many lesions had healed with depressed varioliform and boxcar-like scars. Dermoscopy of dome-shaped active papules showed structureless yellow-red areas, follicular plugs, and in-focus telangiectasias (Figure 1, A and D). The latter were most prominent peripherally but were also seen centrally. Few lesions showed a central white stellate region. Early depressed scars showed in-focus marginal telangiectasias (Figure 1, B and E). Elongated plaques over neck showed similar features of yellow-red structureless areas and white areas suggestive of early scarring in a linear pattern, along with short linear and branching vessels arranged radially (Figure 1, C and F). Histopathology showed multiple perifollicular necrotizing epithelioid cell granulomas in the dermis consistent with LMDF (Figure 2, A and B).

Conclusions

LMDF presents as multiple skin-colored to erythematous fleshy papules and plaques over cheeks, periorcular and perioral regions, especially over eyelids and earlobes. At neck, they present as elongated plaques. Lesions resolve spontaneously in 1-2 years or faster with treatment, leaving depressed, atrophic, varioliform scars.
Figure 1. (A) Erythematous to skin-colored papules over upper and lower eyelid, with middle papule showing central depression. (B) Multiple depressed erythematous scars over the right cheek. (C) Linear erythematous elevated plaques over the right side of neck with background erythema. (D) Dermoscopy of lesions circled in A, showing follicular plug (blue arrow), peripheral in-focus telangiectasias extending to the central region (dotted arrow); white central follicular scar is also seen. (E) Telangiectasias are seen in all lesions corresponding to depressed scars in B, with a central white follicular scar. It is classically stellate, seen in lesion marked as an asterisk. (F) Linear yellowish region (asterisk) and multiple in-focus short linear and linear branching vessels along the lesion (black arrows).
Histopathologically, LMDF is characterized by follicular plugs and a superficial dermal perifollicular granulomatous infiltrate with or without caseation. Late lesions show extensive perifollicular fibrosis.

Dermoscopic features include follicular plugs, some resembling a target surrounding the center, with short linear and linear-branching vessels on an orange-yellow/erythematous background. Different stages of lesions have different dermoscopic features. With chronicity, there is an increase in follicular plugs and perifollicular scaling. The yellow perifollicular background is replaced by white structures in late lesions, corresponding to fibrosis replacing the granulomas [1].

Dermoscopic findings of LMDF differ from other papular granulomatous facial disorders, such as papular sarcoidosis, granulomatous rosacea, lupus vulgaris, and post-kala-azar dermal leishmaniasis (Table 1). Papular sarcoidosis shows orange-yellow structureless areas and does not show follicular plugs and stellate scars. Granulomatous rosacea shows vascular polygons not seen in LMDF.

Our case showed structureless yellow-orange regions, follicular plugs, and white structures as previously described [2]. In addition to documenting these features in elongated plaques, we were able to see in-focus telangiectasias, both in inflammatory lesions as well as in lesions evolving into depressed scars. Some of these vessels were reaching the center of the lesions. Earlier reports have noted unfocussed arborizing, comma-shaped and linear vessels. Yellow areas and vascular changes were readily seen in our patient despite a darker skin phenotype. However, these observations are from one case and may be extrapolated if noted in more patients.

![Figure 2](image)

**Figure 2.** Histopathological examination of facial papule showing features of lupus miliaris disseminates faciei. (A) Irregular acanthosis of the epidermis and dermal perifollicular dense infiltrate with epithelioid cell granulomas (arrowhead) (H&E, ×100). (B) Higher magnification; the infiltrate is composed of lymphocytes, epithelioid cells, and Langhans giant cells (arrow) (H&E, ×400).

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dermoscopic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>Orange-yellow structureless areas with well-focused linear and branching vessels; white scar-like depigmented areas</td>
</tr>
<tr>
<td>Granulomatous rosacea</td>
<td>Linear reddish-violaceous vessels arranged in polygonal network with diffuse or localized orange areas</td>
</tr>
<tr>
<td>Lupus vulgaris</td>
<td>Yellowish-white globules, milia-like cysts, white structureless areas</td>
</tr>
<tr>
<td></td>
<td>Pinkish red background, with telangiectasias (linear, branching)</td>
</tr>
<tr>
<td></td>
<td>White scales, shiny white streaks, white rosettes</td>
</tr>
<tr>
<td></td>
<td>A bluish hue may be seen</td>
</tr>
<tr>
<td>Post-kala-azar dermal leishmaniasis</td>
<td>Multiple yellow tears and erythema</td>
</tr>
<tr>
<td>Granuloma faciale</td>
<td>Translucent white-gray background with whitish streaks and linear telangiectasia</td>
</tr>
</tbody>
</table>
Dermoscopic features of LMDF lesions vary with time and can include in-focus telangiectasias in all stages of evolution, including early scars.

**Informed consent:** Written informed consent for publication of clinical details and clinical images was obtained from the patient.

**References**


Gorlin Syndrome: Sequential Digital Dermoscopy of Palpebral Basal Cell Carcinomas in a Patient Treated with Vismodegib

Luis Mena-Vergara¹, Mariana Silva-Astorga¹, Carolina Carrasco-Cancino¹, Leoncio Muñoz-Uslar²

¹ Department of Dermatology, Faculty of Medicine, University of Chile, Santiago, Chile
² Dermatology Service, Hospital del Salvador, Santiago, Chile

Key words: Gorlin syndrome, digital dermoscopy, palpebral basal cell carcinoma, vismodegib


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Corresponding author: Mariana Silva Astorga, Department of Dermatology, University of Chile, Santiago, Chile.
E-mail: valesilva.astorga@gmail.com

Introduction

Gorlin-Goltz syndrome (GS) is a multi-system genetic disorder, characterized by the development of jaw keratocystic odontogenic tumors (KOT) and multiple basal cell carcinoma (BCC) at young ages. Patients inherit a defective copy of PTCH1, a tumor suppressor gene, responsible for hedgehog pathway signaling (HPS) inhibition. PTCH1 mutations and loss of the remaining wild-type allele are also exhibited in >90% of sporadic BCCs [1]. While most cases are amenable to surgery, locally advanced BCCs and unresectable tumors represent a complex scenario, in which HPS inhibitors may be a feasible treatment option with better clinical outcomes [1]. Digital images can be useful in following up BCC response to treatment [2].

We describe the involution of BCCs dermoscopic criteria recorded with sequential digital dermoscopy (SDD), in a patient with GS during treatment with vismodegib.

Case Presentation

A 58-year-old man with GS diagnosed at age of 7 years, presented with over 50 tumoral lesions and the presence of multiple BCCs in both eyelids was noted (Figure 1A). He had history of several surgical interventions to remove KOTs and BCCs with torpid evolution and development of retractile scars that in turn required advanced plastic surgical treatment to maintain functionality, resulting in aesthetic alterations (Figure 1A). Due to the high risk of causing severe ocular morbidity with a new surgery, vismodegib was initiated, resulting in a significant clinical response after 2 months. SSD was performed before and during treatment, and it revealed shrinking of palpebral tumors and regression of dermoscopic structures (Figures 1 and 2).
Figure 1. (A) Retractile scars due to several surgical interventions with secondary bilateral ectropion and ptosis. Multiple BCCs involving the scalp and periocular area (white arrows). (B) Pigmented BCC in superior left eyelid before vismodegib: typical dermoscopic structures, blue-gray globules, ovoid nest and arborizing vessels (blue arrow). (C) Week 2: Disappearance of some globules (white circle) and less notorious telangiectasia (blue arrows). (D) Week 7: Arborizing vessels are no longer visible (blue circle). (E) Week 8: Notable regression of BCC structures; only a few blue-gray globules persist.

Figure 2. Nonpigmented basal cell carcinoma (BCC) in superior left eyelid. (A) Before vismodegib. Dermoscopic structures of a nonpigmented BCC: Multiple fine telangiectasia (red circle), crusting (blue arrows), whitish unstructured zones (green arrows). (B) Week 2: Notable less crusting and shrinking of whitish unstructured areas (green stars). (C) Week 7: A few fine telangiectasias persist, whitish areas are no longer visible, and some white shiny lines can be identified (black arrows). (D) Week 8: Almost no white lines and vessels remain.
Conclusions

The presence of multiple BCCs is a hallmark finding in GS [1]. BCC accounts for 90% of malignant periocular tumors and represents 4.4%-18.0% of all BCCs [1]. Most periocular BCCs are curable with surgery; however, in patients with more extensive involvement, a surgical resection with curative intent may lead to substantial morbidity or deformity because of the need to remove periocular or orbital tissues that results in reduced functionality and quality of life [1]. Other therapeutic modalities such as photodynamic therapy and topical medications have been used as treatments for small or superficial BCCs. Radiotherapy should be avoided in GS [1].

Vismodegib is a first-in-class inhibitor of the HPS, and it reduces BCC tumor burden and blocks the growth of new BCCs in patients with GS [1]. Vismodegib has shown superior outcomes compared to other therapies; however, complete histologic clearance is not always achieved, and risk of progression or recurrence has been described after treatment cessation [1]. SDD is used for monitoring BCCs response to topical chemotherapy [2]. The presence or disappearance of BCC dermoscopic criteria correlates with tumor persistence or histopathologic clearance respectively [2]. Blue-gray globules and ovoid nests can be detected for a longer period of time, whereas other typical structures decrease in size and number after chemotherapy initiation [2]. There is lack of evidence about SDD of BCCs in patients with GS treated with vismodegib.

SDD may help in detecting subtle changes and in facilitating the diagnosis of recurrence or progression of BCCs in patients treated with vismodegib or alternative treatments other than surgery.

References

Rosette-like Structure: A Main Dermoscopic Feature in a Small Trichilemmal Cyst

Giulia Bazzacco1, Enrico Zelin1, Carlo Alberto Maronese2, Vittorio Ramella3, Diego Signoretto4, Iris Zalaudek1, Nicola Di Meo1

1 Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste, Italy
2 Dermatology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy
3 Plastic Surgery Department, Cattinara Hospital, ASUGI, Trieste, Italy
4 Pathological Anatomy and Histology Department, Cattinara Hospital, University of Trieste, Trieste, Italy.

Key words: trichilemmal cyst, rosette, dermoscopy


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Corresponding author: Enrico Zelin, MD, Dermatology Clinic, Hospital Maggiore, Trieste, Italy. E-mail address: enrico.zelin@gmail.com

Introduction

Trichilemmal cysts (TCs), also called pilar cysts, represent the second most common type of cutaneous cysts, after epidermal ones [1]. TCs most commonly occur in middle-aged women and have a predilection for the scalp but can occasionally show different locations. They appear as solitary or multiple intradermal palpable papules/nodules, occurring as sporadic lesions or in hereditary/familial settings with autosomal dominant transmission [1]. From a histological point of view, TCs have an undulating epithelial wall with no granular layer and a compact keratinization and reveal an isthmic origin [1].

Case Presentation

A 36-year-old woman was referred to our clinic with an asymptomatic papule of 1 mm in diameter above her right eyebrow that relapsed after treatment with cryotherapy, in absence of other skin lesions (Figure 1A). On dermoscopy, shiny white areas arranged as a four-leaf clover (rosette-like structure) with a minimal erythematous background was seen (Figure 1B). The lesion was excised, and histopathological examination indicated a multilayer cystic neoformation with eosinophilic cells positive for high molecular weight cytokeratin (CK34Be12+) and absence of the granular layer, consistent with the diagnosis of TC (Figure 2, A-C).

On clinical examination, TCs appear as smooth, mobile, firm, dermal or subcutaneous papules or nodules with a typical diameter of 10-20 mm. They do not characteristically present visible pores [1]. Dermoscopy usually shows a pinkish-yellow or homogeneous yellowish-white area with a peripheral erythematous halo and sometimes, due to the Tyndall effect, the keratin material appears blueish [1]. In the present case, the TC was very small (1 mm papule) and
showed a white shiny rosette-like structure on dermoscopic evaluation. In the literature, the precise morphological correlate of rosettes is not known, since they are not specific and can be seen in various cutaneous lesions, mainly in actinic keratoses, basal cell carcinomas and squamous cell carcinomas, and rarely in cysts. This rosette-like pattern can be probably caused by horny material in the adnexal opening or by concentric perifollicular fibrosis [2].

Conclusions
Differential diagnosis of TCs can include various entities, such as other cystic lesions but also basal cell carcinoma, squamous cell carcinoma, sebaceous hyperplasia and syringoma (Table 1) [2]. Moreover, these cysts can be subject to inflammation, infection, and enlargement, but rarely grow more extensively, forming proliferating TCs (adnexal tumors

![Figure 1](image1.png)

**Figure 1.** Clinical and dermoscopic appearance of the trichilemmal cyst. (A) A small 1-mm papule above the eyebrow of the patient. (B) Dermoscopy shows shiny white areas arranged as a four-leaf clover (rosette-like structure) with a minimal erythematous background.

![Figure 2](image2.png)

**Figure 2.** Histopathological features of the trichilemmal cyst. (A) Global appearance of the multilayer cystic neoformation, H&E, ×10. (B) Eosinophilic cells and absence of granular layer, H&E, ×40. (C) Cells showing positive immunohistochemistry stain for high molecular weight cytokeratin CK34Be12+, ×40.
**Table 1. Dermoscopic Clues That Differentiate Trichilemmal Cyst from its Main Differential Diagnoses**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Classic Dermoscopic Criteria</th>
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<tbody>
<tr>
<td>Trichilemmal cyst</td>
<td>Pinkish-yellow or homogeneous yellowish-white background</td>
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<td></td>
<td>Peripheral erythematous halo</td>
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<tr>
<td></td>
<td>Absence of pore sign</td>
</tr>
<tr>
<td></td>
<td>Blue pigmentation (Tyndall effect of keratin)</td>
</tr>
<tr>
<td>Epidermal cyst</td>
<td>Yellowish-white papule</td>
</tr>
<tr>
<td></td>
<td>Pore sign: keratin-filled, circular orifice, whitish, yellow, brown or black in color</td>
</tr>
<tr>
<td></td>
<td>Wobble sign (movement of the lesion with respect to the surrounding tissues, except for the pore, which represents the site of anchorage of the cyst)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>Arborizing vessels, sort fine telangiectasias</td>
</tr>
<tr>
<td></td>
<td>Ulceration, erosions</td>
</tr>
<tr>
<td></td>
<td>Maple-leaf like, spoke-wheel and concentric structures</td>
</tr>
<tr>
<td></td>
<td>Blue-gray globules, blue-ovoid nests</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Presence of keratin, especially in conjunction with blood spots</td>
</tr>
<tr>
<td></td>
<td>Coiled vessels</td>
</tr>
<tr>
<td></td>
<td>White structureless zones, white circles (highly differentiated SCCs)</td>
</tr>
<tr>
<td></td>
<td>Predominantly red color, bleeding and ulcerations (poorly differentiated SCCs)</td>
</tr>
<tr>
<td>Syringoma</td>
<td>Yellowish-brownish structures</td>
</tr>
<tr>
<td></td>
<td>Structureless background</td>
</tr>
<tr>
<td></td>
<td>Reticular vessels</td>
</tr>
<tr>
<td>Sebaceous hyperplasia</td>
<td>Central umbilication surrounded by aggregated polylobular white-yellowish structures (cumulus sign); this global appearance is known as bonbon toffee sign</td>
</tr>
<tr>
<td></td>
<td>Surrounding crown of vessels at the periphery</td>
</tr>
</tbody>
</table>

SCC = squamous cell carcinoma.

usually with a benign behavior) or may even undergo malignant transformation. Therefore, when there is suspicion of TC, it is appropriate to proceed to radical surgical excision with histological examination in order to exclude malignant tumors and prevent complications.

In conclusion, dermoscopy represents a noninvasive tool that allows the identification of specific morphological features in different skin tumors. It significantly improves the early diagnosis of cutaneous lesions and helps in choosing the best treatment options for each case based on the suspected diagnosis. In this article, we described a very characteristic dermoscopic pattern associated with a small TC. The prompt surgical treatment and subsequent histopathological examination aided in a diagnosis of certainty and in prevented the growth of this lesion that was localized to an aesthetic area.

**Informed consent:** Written informed consent for publication of her clinical details and clinical images was obtained from the patient.

**References**


Syphilitic Balanitis of Follmann: Can Dermoscopy Be Useful Tool in the Differential Diagnosis?

Roberta Vezzoni¹, Claudia Colli², Giacomo Rebez³, Carlo Trombetta³, Andrea Boltar³, Iris Zalaudek¹, Claudio Conforti¹

1 Dermatology Clinic, University of Trieste, Ospedale Maggiore di Trieste, Italy
2 MST Centre, ASUGI, Trieste, Italy
3 Department of Urology, University of Trieste, ASUGI, Trieste, Italy

Key words: syphilitic balanitis of Follmann, dermoscopy, dermatology, urology, sexually transmitted diseases


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Corresponding author: Claudio Conforti, MD, Dermatology Clinic, Maggiore Hospital of Trieste, Trieste, Italy.
E-mail: Claudioconforti@yahoo.com

Introduction

Syphilis is a sexually transmitted infection caused by the spirochete Treponema pallidum that has different clinical presentations. Among them, there is Follmann balanitis, that was first described by Eugene Follmann in 1948. It is a rare manifestation of primary syphilis that presents as erosive balanitis [1]. Herein we report the dermoscopic description of a Follmann balanitis and discuss how to differentiate it from other sexually transmitted or genital diseases.

Case Presentation

A previously healthy 28-year-old man was admitted to the Urology Department for the presence of painless erosions on the glans and erythema. He was initially treated with topical antibiotics and steroids but without benefit. Physical examination revealed painless crusted erosions of the glans and foreskin associated with edema and ulceration of the coronal sulcus (Figure 1A). Dermoscopy revealed the presence of homogeneously distributed glomerular vessels and focused linear curved vessels on an erythematous background with hyperpigmented post-inflammatory areas (Figure 1B). Bilateral inguinal lymphadenopathy was also observed. The patient reported a high-risk sexual contact 2 months earlier. A polymerase chain reaction test performed for common sexually transmitted diseases was negative. Serological tests for syphilis were positive: VDRL 1:32 and TPHA 1:1280. Based on these results, a diagnosis of Follmann syphilitic balanitis was made. The first choice of treatment for primary syphilis is a single intramuscular injection of 2.4 million units of benzathine-penicillin, but due to allergy reported by the patient, treatment with doxycycline 100 mg twice daily for 14 days was started. At the one-month follow-up visit, complete healing of the glans was observed.
Conclusions

The clinical features of syphilitic balanitis or balanoposthitis are variable, as they can manifest as an edematous balanitis with erosions and crusted lesions or as a papular form with smooth white/pink coalescent papules and plaques on the surface of the glans. Common clinical manifestations are the hardening of the glans penis and bilateral inguinal lymphadenopathy [1].

The differential diagnosis requires the exclusion of infectious such as Candida albicans, groups B and D Streptococci and herpes simplex virus, and noninfectious diseases such as lichen sclerosus et atrophicus, Zoon balanitis, psoriasis, eczema, fixed drug rash and erythroplasia of Queyrat (EQ). Even if dermoscopy is not the gold standard test for the diagnosis, it is a useful tool in the differential diagnosis. Candidal balanitis is characterized by cottage cheese-like structures and blurry linear vessels, psoriasis is defined by a quite monomorphic pattern with diffusely distributed dotted vessels. On the other hand, glomerular vessels are a constant finding in EQ while focused linear curved vessels and orange structureless areas are dermoscopic findings of Zoon balanitis [2]. In our case, the presence of glomerular and hairpin vessels on an erythematous background without other typical signs of other pathologies helped us to exclude the differential hypotheses reported above.

Follmann erosive balanitis may be the only clinical expression of primary syphilis, so it is essential to include this rare clinical manifestation in the differential diagnosis of balanitis and balanoposthitis [1]. Dermoscopy could be an extremely useful tool that can direct the experienced clinician towards the correct diagnosis and allow proper treatment.

**Informed consent:** Written informed consent for publication of clinical details and clinical images was obtained from the patient.

References

Umbilical Endometriosis: A New Dermoscopic Pattern

Jorge Juan Vega-Castillo¹, Soledad Saenz-Guirado¹, Maria Luisa Vega-Castillo², Ricardo Ruiz-Villaverde¹

¹Dermatology Department, Hospital Universitario San Cecilio, Granada, Spain
²Ophtalmology Department, Hospital de Alta Resolución de Écija, Spain

Key words: endometriosis, pattern, dermoscopy


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Corresponding author: Ricardo Ruiz-Villaverde, Unidad de Dermatología. Hospital Universitario San Cecilio, Granada, Spain.
E-mail: ismenios2005@gmail.com

Introduction

Endometriosis is defined as the growth of ectopic endometrial tissue outside the uterine cavity. Extra pelvic endometriosis occurs in 12% of women, and umbilical endometriosis, a rare presentation of extra pelvic endometriosis, occurs in 0.5%-1% of reported cases. Umbilical endometriosis is also known as Villar nodule as Villar first described the condition in 1886. Cutaneous endometriosis tends to settle on scars from surgical procedures (abdominal or pelvic surgery) such as hysterectomy, caesarean section, laparoscopy, or episiotomy. From a clinical point of view, it is necessary to establish a differential diagnosis with amelanotic melanoma, basal cell carcinoma, Sister Mary Joseph nodule, or pyogenic granuloma.

Case Presentation

A 45-year-old woman attended our dermatologic outpatient clinic complaining of a 4-months history of a solitary painless umbilical nodule. The bluish-green colored lesion had not appeared on a previous scar. Any recent bleeding episode was ruled out. A complete medical history revealed long-term dysmenorrhea as the only relevant clinical finding. On dermoscopy, a central white reticular pattern on a violet background was observed (Figure 1A). No vascular structures, points, globules, or structures suggestive of a melanocytic lesion were observed. Histopathological examination was consistent with cutaneous endometriosis (Figure 1B). Complementary tests, including abdominal-pelvic CT and determination of cancer antigen 125 offered results within normal ranges.

Conclusions

There are few dermoscopic descriptions in the literature of cutaneous endometriosis [1,2]. The main dermoscopic findings and histopathological correlation are reflected in Table 1. There appears to be a difference in patterns depending on the phase of the hormonal cycle, as well as the depth of the lesion, histological subtype and phototype of the patient.
Table 1. Dermoscopic Descriptions of Umbilical Endometriosis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Dermatoscope Model</th>
<th>Dermoscopic Features</th>
<th>Interpretation</th>
<th>Polarized Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa, 2014 [5]</td>
<td>DermLite DL3,</td>
<td>Polypoid projections of erythematous violaceous color, area with dark brown globules and area of active bleeding (mid follicular phase) Increased in both characteristics (luteal phase)</td>
<td>Endometrial atrophy Hemoglobin degradation after bleeding period, corresponding to hemosiderin deposits</td>
<td>Polarized light dermoscopy</td>
</tr>
<tr>
<td>Bonné, 2020 [2]</td>
<td>DermLite DL4</td>
<td>Umbilical endometriosis (polypoid structure) with drainage openings</td>
<td>Multiple irregular glands with erythrocytes and drainage openings</td>
<td>Polarized light dermoscopy</td>
</tr>
<tr>
<td>Sandoval, 2021 [6]</td>
<td>Unknown</td>
<td>Pink homogeneous lesion with a focal bluish blotch/clod</td>
<td>Hemosiderin deposits</td>
<td>Polarized light dermoscopy</td>
</tr>
</tbody>
</table>

White reticular pattern (negative pigment network) is due to elongated rete ridges and is characteristic of melanoma. Nevertheless, it has also been observed in Spitz/Reed nevi. The diffuse area of bluish color is likely related to hemosiderin deposits, unlike the referred deposits observed in other cases reported as small focused globules.

Histopathological examination remains the diagnostic gold standard for endometriosis. It is considered mandatory in ruling out a neoplastic condition, as more than 60% of umbilical tumors are malignant. The description of new dermoscopic patterns and their histological correlations can be helpful in the diagnosis of this entity.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.

References


Ablative Fractional Erbium:YAG Laser Resurfacing: A Treatment Option for Acne

Stefania Guida¹, Nicola Lippolis¹, Matteo Giovani¹, Gioia Pedroni¹, Giacomo Giovanni Urtis², Giovanni Pellacani¹,³, Francesca Farnetani¹, Marco Manfredini¹

¹Dermatology Unit, Department of Surgical, Medical, Dental and Morphological Science with Interest Transplant, Oncological and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
²Cliniche Diventa, Milano-Roma-Como, Italy
³Dermatology Clinic, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

Key words: acne, laser, erbium:YAG, active acne


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Corresponding author: Dr Nicola Lippolis, Dermatology Unit, Department of Surgical, Medical, Dental and Morphological Science with Interest Transplant, Oncological and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy. E-mail: lippolismicol@gmail.com

Introduction

Acne vulgaris is a disease of the pilosebaceous unit, characterized by a hyper keratinization process, comedo formation, and inflammatory reactions [1]. The use of lasers for the treatment of acne has been described, but the role of resurfacing lasers for active acne has not been clarified yet.

Case Presentation

We present the cases of 3 women with noninflammatory and inflammatory acne lesions. They received laser therapy because they refused prolonged topical treatments or other systemic acne therapies. No treatment was given to the patients in the previous 6 months prior to laser treatment. The patients gave informed consent to mild laser rejuvenation therapy with ablative fractionated erbium:YAG laser, (Xlase plus; Biotec Italia srl, Dueville, VI).

These patients were treated using the standard protocol for mild resurfacing and rejuvenation. Employed parameters were 1.5 ms, 3.5 mJ/cm², 5 Hz on the cheeks and the chin, and the rest of the face was treated with 1.0 ms, 2.8 mJ/cm², 6 Hz. One laser session per month for 3 months was performed for each patient. Overlapping pulses were performed over inflammatory lesions. After the laser sessions, the patients were instructed to apply sunscreen SPF 50+ and a hydrating cream for 30 days. All 3 patients tolerated the treatment without any reported side effects. They showed a visible improvement of the skin texture and a reduction of active acne.
The average value for the Investigator Global Assessment scale (IGA) was indicative of a mild-moderate acne at baseline (IGA 1-2) and decreased consistently to the almost-clear stage (IGA 0-1) at the last follow-up visit 3 months after the last laser session (Figures 1 and 2).

One paper describes the application of multiple sessions of erbium:YAG laser treatment for active acne on 2 patients with inflamed cystic acne [2]. Singh et al hypothesized that the mechanism of action of this laser source might be related to the photothermal effect acting on follicular hyperkeratosis and contributing to skin microbe modulation.

The short follow-up period of our patients represents a limitation of this case report. Further studies are needed to investigate the anti-acne effect of erbium: YAG laser and its mechanism of action with respect to comedogenesis and inflammation.

**Conclusions**

Acne is one of the most common skin diseases. Many therapeutic approaches are currently available for active acne, including laser treatments. However, the role of resurfacing

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**Figure 1.** Clinical pictures of a 34-year-old woman. (A) Before the last erbium:YAG laser session. (B) 3 months after the last erbium:YAG laser session, showing the reduction of active acne lesions.

**Figure 2.** Clinical pictures of a 25-year-old woman. (A) Before the last erbium:YAG laser session. (B) 3 months after the last erbium:YAG laser session, highlighting a consistent reduction of both inflammatory and noninflammatory acne skin lesions.
with erbium:YAG laser has not been clarified yet. Results from clinical practice, such as in the cases presented herein, highlight the importance of further investigations in this field.

**Informed consent:** Written informed consent for publication of their clinical details and clinical images was obtained from all patients.

**References**


Trichofolliculoma Mimicking Squamous Cell Carcinoma

Ahmed Abdelbary¹, Hadir Shakshouk¹

¹Department of Dermatology, Andrology and Venerology, Alexandria University, Egypt

Key words: trichofolliculoma, adnexal tumors, hamartoma, dermoscopy, case report


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Corresponding author: Hadir Shakshouk, MBBS, MSc, Department of Dermatology, Andrology and Venerology, Alexandria University, Egypt. E-mail: drhadir58@gmail.com

Introduction

Trichofolliculoma, a rare follicular hamartoma, manifests itself as a solitary papule or nodule in adults involving the head and neck region. It is characterized by a single primary cystic structure from which radiates numerous secondary hair follicles. While dermoscopy has been widely used as a diagnostic tool, dermoscopic features of adnexal lesions are poorly described owing to their rarity and inadequate reporting.

Case Presentation

We describe a 75-year-old male patient who presented with asymptomatic solitary nodule on the forehead of 2-years duration. Upon examination, a single nodule of 1 cm diameter with central crust and raised border was noted on his forehead (Figure 1A). Dermoscopic evaluation revealed a nodule with central crusting, multiple fine linear vessels, and whitish circles mainly on the margin (Figure 1B).

These features were highly suggestive of squamous cell carcinoma. However, histopathological examination demonstrated multiple cystically dilated follicular infundibula lined by stratified squamous epithelium with numerous vellus hair follicles originating from them. Multiple lobules of follicles of varying maturity were observed radiating from these dilated follicular infundibula. Some showed sebaceous glands. A fibrocellular stroma surrounding the tumor was noted (Figure 1C). Thus, a diagnosis of trichofolliculoma was made.

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

Conclusions

Trichofolliculoma is considered to be a rare follicular hamartoma that classically manifests as a papule or nodule with a central dilated pore and tufted hairs. This presentation corresponds histopathologically to a central primary follicle with many radiating secondary vellus hair follicles.
While thought to be diagnostic for trichofolliculoma, few cases demonstrate central hair tufting. The lack of a central hair plug, as in our case, renders the clinical diagnosis challenging.

Dermoscopy of trichofolliculoma is not well described in literature. Panasiti et al reported a patient with single nodule suspicious for basal cell carcinoma [1]. However, dermoscopic examination revealed a central brown zone with radial brown projections without pigment network, which was described by the authors as a “firework” pattern. These projections correlated histopathologically with the nests of cells radiating from a follicular epithelium [1]. Garcia-Garcia and colleagues described different dermoscopic features that included a well-defined bluish nodule with a white-pink central area, shiny white structures, dotted vessels, and a central scale in one patient [2]. Histopathologically, the early stages demonstrated few secondary vellus hair follicles originating from a primary follicle, whereas mature lesions showed increased number of vellus hair follicles. In later stages, thickened primary follicle with fewer secondary follicles could be seen [2].

Trichofolliculoma classically presents with a hair plug emanating from the center of a nodule; however, hair plug may be absent in many cases, making the diagnosis challenging. In these cases, other serious diagnoses should be ruled out. Dermoscopy of trichofolliculoma is poorly described in the literature. We introduce the possibility of new dermoscopic findings of trichofolliculoma.

References
Bullous Erythema Nodosum Leprosum Through the Dermoscope

Deepak Vashisht¹, Shekhar Neema¹, Durga Madhab Tripathy¹, Prashant Sengupta²

¹ Department of Dermatology, Armed Forces Medical College, Pune, India
² Department of Pathology, Armed Forces Medical College, Pune, India

Key words: bullous ENL, dermoscopy


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Corresponding author: Durga Madhab Tripathy, Senior Resident, Department of Dermatology, Armed Forces Medical College, Pune, India.
E-mail: dmt5861@gmail.com

Introduction

Erythema nodosum leprosum (ENL) forms a part of type 2 leprosy reaction characterized by crops of tender evanescent erythematous nodules that appear on extensors accompanied by systemic symptoms like fever and arthritis. Bullous ENL is a rare variant of the type 2 reaction characterized by multiple vesicles and flaccid bullae at sites of classic ENL with severe systemic symptoms. Other atypical variants include necrotic, hemorrhagic, purpuric, Sweet syndrome-like and erythema multiforme-like ENL.

Nowadays, dermoscopy is routinely employed in the diagnosis of leprosy, and it shows features akin to granulomatous dermatoses, explicitly, yellow-orange background reminiscent of underlying granulomas and few specific features. Specific features in the tuberculoid pole include loss of appendages and in the lepromatous pole xerosis, scaling, and hypopigmentation. Leprosy reactions are characterized by vascular changes in the form of arborizing blood vessels in ENL and diffuse erythema in type 1 reaction [1].

We report dermoscopic findings of bullous ENL lesions in a patient, findings that revealed both typical and atypical features.

Case Presentation

A 37-year-old male, with a known case of Hansen disease (borderline lepromatous leprosy) and on multidrug therapy consisting of rifampicin 600 mg monthly, dapsone 100 mg and clofazimine 50 mg daily for 1 year, presented with multiple red raised, painful, erythematous nodules distributed symmetrically over the face, back, and upper limbs. Vesicles and bullae containing clear fluid were superimposed on most lesions (Figure 1, A and B). There was associated redness of the eyes, a high-grade fever, and joint pains. Mucosal surfaces, palms and soles were not involved, and Nikolsky sign was negative.

Tzanck smear showed neutrophils, and acantholytic cells were absent. A slit-skin smear test for acid-fast bacilli (Mycobacterium leprae) from 8 different sites, including
lesions, showed an average bacteriological index of 4+. Histopathology of the involved skin showed an intraepidermal separation, spongiosis, and neutrophilic infiltrate. Multiple ill-formed granulomas comprising of epithelioid cells, lymphocytes, and foamy histiocytes were noted surrounding the dermal nerves and appendages (Figure 2, A and B). Dermoscopy was performed using handheld DermLite DL4 dermatoscope, and images were captured with a Samsung phone. It showed a homogeneous white-pink area with an irregular border and surrounding erythema, similar to findings mentioned in the literature [2]. A closer view showed a few atypical and novel features in the form of a crumpled fabric appearance of white-pink areas and brown-gray dots and globules at the periphery (Figure 3, A and B).

The patient was managed as a type 2 leprosy reaction (bullous ENL) with prednisolone 40 mg/day and thalidomide 100 mg 4 times a day. He responded to treatment and is currently on tapering doses of steroids and thalidomide.

**Conclusions**

Leprosy has always eluded dermatologists with its varied presentations, and bullous ENL is an excellent example. With the growing popularity of dermoscopy in the diagnosis of
leprosy, we tried to analyze dermoscopic findings of bullous ENL lesions. The novelty of this case lies in intriguing clinical aspects and newer perspectives through the dermoscope.

**Informed consent:** Written informed consent for publication of clinical details and clinical images was obtained from the patient.

**References**


Gorlin Goltz Syndrome: Beware of Melanoma

Filomena Russo¹, Flavio Giulio Liso¹, Francesco Santi¹, Luca Provvidenziale¹, Paolo Taddeucci¹, Pietro Rubegni¹

¹Department of Medical, Surgical and Neurological Science, Dermatology Section, University of Siena, S. Maria alle Scotte Hospital, Siena, Italy

Key words: Gorlin Goltz syndrome, melanoma, reflectance confocal microscopy, dermoscopy


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Corresponding author: Francesco Santi, MD, Dermatology Section, University of Siena, S. Maria alle Scotte Hospital, Siena, Italy. E-mail: santi-francesco90@gmail.com

Introduction

Gorlin Goltz syndrome, also known as basal cell nevus syndrome, is a rare autosomal dominant multisystem disorder. The “signature” feature of Gorlin Goltz syndrome is an earlier onset and a higher number of Basal Cell Carcinomas (BCC), median of 160 BCCs in an average lifetime [1]. The genetic base of this syndrome is mainly to be found in pathologic constitutive activation of the Sonic Hedgehog signaling pathway. Patients with this syndrome, beyond numerous BCCs, can also present a wide spectrum of manifestations such as: jaw odontogenic keratocysts, palmoplantar pits, lamellar calcification of the falx cerebri, skeletal abnormalities, childhood medulloblastomas and cardiac or ovarian fibromas.

Case Presentation

A 60-year-old Caucasian woman was referred to our department because she had been diagnosed with Gorlin Goltz syndrome, with a 20-year history of multiple BCCs predominantly involving her face and upper back as well as multiple jaw cysts. After she had undergone multiple surgical procedures, she started vismodegib with a daily dose of 150 mg from November 2019. Clinical follow-up after 3 months showed progressive improvement in the size of the lesions. On a further follow-up visit in March 2020, the patient continued to show improvement, but a 7-mm pigmented oval-shaped lesion was noted on her scalp (Figure 1A). On 20x polarized dermoscopy regression structures, irregular dark blue pigmented blotches and a brownish peripheral network reminiscent of leaf-like structures were seen, leading to a possible diagnosis of BCC versus melanoma (Figure 1B). However, reflectance confocal microscopy (RCM, Vivascope 3000, Caliber) examination showed pagetoid infiltration of round and dendritic atypical cells in the epidermis and irregular meshwork at the dermo-epidermal junction (Figure 1C), suggesting the diagnosis of melanoma. An excisional biopsy was performed, and the histopathological examination revealed an invasive melanoma with 0.48 Breslow thickness with conspicuous regression (>75%).
Conclusion

The presence of melanomas in Gorlin Goltz syndrome is rare and there are only a few documented cases in the literature [2]. Since melanomas of the scalp frequently display nonclassic melanoma dermoscopic criteria they can simulate other tumors, amongst which BCC is one. Indeed, typical dermoscopic features of pigmented basal cell carcinomas such as large blue-gray ovoid nests and arborizing vessels can also be found in melanoma. RCM is able to diagnose BCCs mimicking melanoma at dermoscopy as well as melanoma mimicking BCCs. Typically, BCCs on RCM display the presence of tight basaloid islands, peripheral clefting and increased dermal vasculature whereas melanoma of the scalp usually, under RCM, has irregular meshwork patterns associated with the presence of nests of atypical melanocytes at the dermo-epidermal junction. The systematic use of RCM on these multiple inconspicuous lesions has enabled clinicians to arrive at a diagnosis of BCC or a melanocytic lesion in few minutes, and with a high level of confidence, since clear-cut confocal criteria can be observed. Our case highlights the benefits of using a combined approach between dermoscopy and RCM in Gorlin Goltz syndrome patients to identify ambiguous lesions in order to discriminate melanoma from BCC, and therefore avoid therapeutic errors and allow clinicians to act promptly. Nonetheless this case highlights the importance of performing a complete body examination. Lesions in areas difficult to explore such as the scalp, in particular in non-bald patient where the presence of hair may hinder a quick examination, could be easily failed to spot resulting in a delayed treatment.

References


Giant Congenital Melanocytic Nevi and Poliosis in a 3-day-old Boy: Is It Just a Coincidence?

Ahu Yorulmaz¹, Ayse Akbas¹

¹ Ankara Bilkent City Hospital, Department of Dermatology, Pediatric Dermatology Unit, Ankara, Turkey

Key words: congenital, melanocytic nevi, giant, poliosis, developmental abnormalities

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Corresponding author: Ahu Yorulmaz, Ankara Bilkent City Hospital, Department of Dermatology, Universiteler Ankara. E-mail: ahuyor@gmail.com

Introduction

Giant congenital melanocytic nevi (GCMN) are rare benign nevomelanocytic proliferations that are expected to reach a diameter of at least 20 cm in adulthood. Here, we present a case of GCMN associated with poliosis.

Case Presentation

A 3-day-old baby boy, born of a non-consanguineous marriage, was examined at our pediatric dermatology outpatient clinic for a black nevus on his back. He was otherwise healthy and his family history was unremarkable. We observed a black patch measuring approximately 10 cm × 15 cm in size on the left upper back of the patient. A localized patch of white hair on the occiput and satellite nevi on the face, trunk and extremities of the patient were also noticed (Figure 1). A thorough neurological examination and magnetic resonance imaging of the brain and spine didn’t reveal any pathology. Diagnoses of GCMN and poliosis were made and the patient was taken under follow-up.

Conclusions

This is the third report in the literature describing the coexistence of GCMN and poliosis [1,2]. In 1999 Yosipovitch et al presented a patient with GCMN with poliosis [1] and in 2013 Lee et al reported a patient with GCMN of the scalp with cranial defect, poliosis and hair loss [2]. GCMN have been associated with several developmental abnormalities, including cutis verticis gyrata, limb atrophy/hypertrophy and hamartomas. Postzygotic mutations affecting somatic cells may provide one explanation of the occurrence of these associations. Mutations in NRAS, BRAF, and Tp53 have been specified in congenital melanocytic nevi (CMN) samples. If the mutation develops early enough, it can affect a multipotent progenitor cell, leading not only to CMN in the cutaneous tissue, but also abnormalities in the other organs. Given the accompanying cranial defect and alopecia, Lee et al proposed that the destruction of cranium, hair follicles and bulb melanocytes might have been caused by an inflammatory or autoimmune response, or even the destructive potential of the nevus cells per se [2].
Poliosis, which is defined as a localized patch of white hair within a group of hair follicles, has been described in association with different genetic or acquired conditions, including benign and malignant melanocytic neoplasms. A perifollicular lymphohistiocytic infiltration suggests an inflammatory/autoimmune response as the causative mechanism in the pathogenesis of poliosis in patients with melanocytic lesions. Another suggested theory involves the migration arrest of fetal melanocytes into the hair bulbs. It is well-known that melanoblasts originate from pluripotent precursor neural crest cells, migrate along defined pathways and differentiate into melanocytes.

The fact that poliosis may arise embryogenetically strongly implies the role of genes in the pathogenesis of poliosis associated with GCMN. However, the main question still remains unclear: is poliosis an associated feature of melanocytic lesions or is the coexistence of poliosis and GCMN in the same individual a coincidental finding? If this is a real association, what’s the exact underlying mechanism in the pathogenesis? Further case reports will allow the pathogenesis of the association between GCMN and poliosis to be better understood.

**Informed consent:** Written informed consent for publication of clinical details and clinical images was obtained from the patient’s parents.

**References**


Graham-Little-Piccardi-Lassueur Syndrome With Concomitant Mucocutaneous Lichen Planus: Rare Presentation in a Man

Avita Dhiman¹, Priyanka Sangwan¹, Neirita Hazarika¹, Prashant Durgapal²

1 Department of Dermatology, Venereology and Leprosy, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
2 Department of Pathology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

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Corresponding author: Neirita Hazarika, MD, Additional Professor, Department of Dermatology, Venereology and Leprosy, All India Institute of Medical Sciences, Rishikesh Uttarakhand, India. E-mail: neirita.derma@aiimsrishikesh.edu.in

Introduction

Graham-Little-Piccardi-Lassueur syndrome (GLPLS) described by Piccardi in 1913 is a rare variant of lichen planopilaris, characterized by a triad of multifocal cicatricial alopecia of the scalp, non-cicatricial alopecia of axillae, pubis and lichenoid follicular eruption [1]. The exact etiology is unknown, but cell-mediated immunity may play a role. Over 50% of patients with GLPLS presents with at least 1 episode of cutaneous or mucosal lichen planus (LP) [1]. The progression of GLPLS is variable, and results in irreversible cicatricial alopecia causing significant psychosocial distress [1]. Herein we report a case of GLPLS in a male with mucocutaneous LP and incidental findings of hidradenitis suppurativa (HS) and fixed drug eruption (FDE).

Case Presentation

A male in his late forties presented with progressive loss of scalp hair over thirty years and history of loss of axillary and pubic hair, along with multiple, pruritic, violaceous lesions over face, trunk for the last 6 years. He also complained of pain and burning sensation in his mouth for the past 6 months; associated history of recurrent, multiple, painful swellings in bilateral axillae, groin in the last 2 years; 3 of such episodes occurred in the previous 3 months. He also reported history of 3 episodes of itchy, burning reddish lesion over abdomen, each time after taking painkillers.

Cutaneous examination revealed scarring alopecia of whole scalp with few patches of uninvolved hair in occipital area (Figure 1A) and non-scarring hypotrichosis of axillary, beard area (Figure 1B,1C) and pubic region. Multiple poly-porous comedones and bridging scars were also seen in axillae, (Figure 1B) and groin. Multiple violaceous, flat-topped papules over face (Figure 1C), trunk with lichenoid follicular papules over upper back (Figure 1D) were noted. Buccal mucosa showed whitish, reticular plaques (Figure 1E). Single, well-defined, oval hyperpigmented macule was noted over abdomen (Figure 1F).

Investigations revealed positive serology for hepatitis C virus (HCV) with aspartate aminotransferase level of 131U/L,
alanine aminotransferase 76 U/L, alkaline phosphatase of 301 U/L; other lab values were within normal ranges. Scalp biopsy showed perifollicular lymphocytic inflammation (Figure 2A). Trichoscopy of occipital scalp revealed loss of hair follicles with perifollicular scales, erythema, hyperpigmentation, and peri-pilar casts (Figure 2B). Based on clinical, dermoscopic and histopathological features, a diagnosis of GLPLS with quiescent HS, FDE and concurrent HCV infection was made.

Oral drug provocation test to ascertain cause of FDE was refused by the patient. Dermatological treatment was initiated
with topical tacrolimus for scalp and facial lesions, topical triamcinolone acetonide for oral lesions and clindamycin gel for axillae and groin. Patient was counseled about the permanent hair loss in scalp and to use painkillers with caution. HCV infection was managed by gastroenterology department as per protocol. Monthly follow-up showed moderate improvement in oral and cutaneous lesions of LP, no flare in HS lesions and no further episodes of FDE.

Conclusions

GLPLS is a rare entity. Associations with Hepatitis B virus vaccination, androgen insensitivity, and HLADR-1 genetic susceptibility syndrome have been described [2]. Concomitant HCV infection associated with classical LP was seen in our case. GLPLS predominantly affects middle-aged women [1]; male cases of GLPLS are rare. This case of GLPLS is reported because of extreme rarity of presentation in a male with concomitant HCV infection and incidental findings of HS and FDE.

Informed consent: Written informed consent for publication of clinical details and clinical images was obtained from the patient.

References

Scrotal Basal Cell Carcinoma—A Rare Manifestation

Tugba Kevser Uzuncakmak¹, Defne Özkoca¹, Bengu Cobanoglu Simsek², Server Serdaroglu¹

¹ Istanbul University, Cerrahpasa, Cerrahpasa Medical Faculty Department of Dermatology, Istanbul, Turkey
² Istanbul Medeniyet University Medical Faculty, Department of Pathology, Istanbul, Turkey


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Corresponding author: Tugba Kevser Uzuncakmak, MD, Istanbul University Cerrahpasa Medical Faculty, Department of Dermatology, Istanbul, Turkey. E-mail: drtugbakevser@gmail.com

Case Presentation

A 68-year-old male presented with a 6-year history of a slowly growing ulcerated lesion on the scrotum. Dermatological examination revealed a polypoid lesion of $2 \times 2$ cm on an erythematous base on the left scrotum. The surface was ulcerated, and microbleeding spots were observed (Figure 1, A and B). No other lesions were present. Contact dermatoscopy of the lesion revealed polymorphic linearly grouped dotted vessels and short linear vessels. Surface ulceration was prominent with the rope sign. Crystallite structures were evident in the left lower quadrant. (Figure 1C). The patient was referred for total excision. The histopathology revealed basal cell cancer of metatypical type (Figure 1D). No new lesions were observed in the biannual follow-up visit.

Teaching Point

Basal cell carcinoma is the most common type of cancer that is commonly seen on sun-exposed areas, yet it is rarely seen on the genitalia. Despite its rarity, genital basal cell carcinomas have increased risk of distant metastasis. Therefore, after the initial therapy, long-term follow-up is mandatory in these cases.
References


Figure 1. (A and B) A 2 × 2 cm sized, polypoid, centrally ulcerated tumoral lesion on an erythematous base on the left scrotum. (C) Polymorphic linearly grouped dotted vessels and short linear vessels. Surface ulceration was prominent with the rope sign. (D) Widespread ulceration on the surface. Tumor cells proliferating as nodular structures from the basal layer to the stroma had pale large cytoplasm (H&E, ×100).
Case Presentation

A 17-year-old boy and an 8-year-old boy presented to us with discrete patches of smooth, non-scarring alopecia co-localized with depigmentation over the scalp (Figure 1, A and B). In the first case, alopecia areata followed vitiligo, while it was the opposite in the second case. On dermoscopy of the alopecic patches, black dots, broken hairs, and velvus hairs were appreciated. We made a diagnosis of alopecia areata co-localized with vitiligo based on clinical and dermoscopic findings.

Teaching Point

There are few previous reports of co-localization of alopecia areata and vitiligo [1,2]. They seem to share common pathogenesis; however, it has also been argued that this might be just a coincidence. An interferon (IFN)-γ-driven immune response is proposed in both diseases whereby IFN-γ is required for the recruitment of CD8+ cytotoxic lymphocytes to the sites of inflammation [2]. Class II human leukocyte antigen (HLA) and other non-HLA genes have also been implicated in both diseases [1]. In alopecia areata, the initial targets for autoimmunity are hair follicle melanocytes (along with keratinocytes, and dermal papilla cells) while in vitiligo the initial target is epidermal melanocytes [1]. When this compartmentalization is blurred, both epidermal and hair follicle melanocytes are destroyed by autoimmunity, leading to co-localization.
References


Nevoid Acanthosis Nigricans Located on the Scalp

Jorge Román-Sainz¹, Nicolás Silvestre-Torner¹, Sergio Samer Tabbara-Carrascosa¹, Adrián Imbernón-Moya¹

¹Dermatology Unit, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain

Case Presentation

A 14-year-old male presented with an alopecic plaque in his occipital area. Skin exam revealed a well-defined, hyperpigmented plaque with a velvety texture, resembling acanthosis nigricans (AN) (Figure 1A). Trichoscopy showed broken hair shafts and yellow dots, as well as a few exclamation mark hairs. Histology manifested mild acanthosis, hyperkeratosis, and papillomatosis, with no visible nests of melanocytes (Figure 1B). Due to these findings, the patient was diagnosed with nevoid AN. This skin disorder, also known as RAVEN (round and velvety epidermal nevus) is a rare entity, which appears at or before puberty [1,2].

The skin disorder RAVEN has no predilection for intertriginous or flexural areas. Most reported cases are unilateral and located on the chest, abdomen and umbilical, or retroauricular area. We found no other reports of RAVEN involving the scalp in the literature. As it is a benign condition, RAVEN requires no treatment or follow-up, and has not been found to be associated with any underlying disorder [1,2].

The closest differential diagnosis is with epidermal nevus. Although they are clinically very similar, RAVEN is usually velvetier, and histology plays an essential role as it shows compact hyperkeratosis, papillomatosis and limited acanthosis as compared to epidermal nevi. Other differential diagnosis include confluent and reticulate papillomatosis, ichthyosis hystrix, and the hyperkeratotic type of seborrheic keratosis. In our case, the velvety texture of the lesion, as well as the histology, which showed mild acanthosis, excluded epidermal nevus.

Teaching Point

RAVEN can resemble epidermal nevi or AN. Dermatologists should be aware of this entity and should consider it in the differential diagnosis of pigmented skin lesions.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.
References


Figure 1. (A) Well-defined, hyperpigmented plaque located in the occipital area of the patient, associated with loss of hair density. (B) Histology showing elongated papilla (yellow arrow), acanthosis (green arrow), hypergranulosis (blue arrow) and hyperkeratosis (orange arrow). Melanosis (red arrow) is also visible in some areas.
Protrusions Within a Pink-Yellow Plaque

Csongor Németh¹, Melánia Pozsgai¹, Rolland Gyulai¹, Zsuzsanna Lengyel¹

1 Department of Dermatology, Venerology and Oncodermatology, Medical School, Clinical Center - University of Pécs, Pécs, Hungary


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Corresponding author: Zsuzsanna Lengyel MD, PhD. Department of Dermatology, Venerology and Oncodermatology, Medical School, Clinical Center - University of Pécs, Hungary. E-mail: lengyel.zsuzsanna@pte.hu

Case Presentation

A 74-year-old woman with a history of several skin tumors was referred to our center. She complained of a lesion localized on the right flank, growing for 15 months. Upon examination, a 75 mm × 30 mm pinkish-yellowish plaque was observed. Within the lesion, three red, firm, keratotic papules were seen (Figure 1A). Dermoscopy showed yellow globules with indistinct borders on a whitish-erythematosus background. In the yellowish structures, polymorphous vessels consisting of linear irregular vessels and curved vessels were seen. Within the papules hairpin, coiled vessels were present (Figure 1, B-D).

Due to the large size, an incisional biopsy was performed. Histopathology revealed the collision of an in-situ squamous cell carcinoma and superficial sebaceous carcinoma (SC). The lesion was excised with safety margin. Pathology confirmed the previous diagnosis.

Teaching point

Sebaceous carcinoma tends to mimic squamous and basal cell carcinomas. The presence of yellowish structures and polymorphous vessels are features suggestive of SC. Some suggest that extraocular SC might originate from preexisting intraepidermal squamous neoplasia [1,2].

Informed consent: Written informed consent for publication of clinical details and clinical images was obtained from the patient.
References


Scalp Pink Tumors Showing Multiple Rosettes

Karla Patricia Estrada-Ramírez¹, Denisse Herrera-Bringas², Maribet González-González³, Daniel Alcalá-Pérez²

¹ Department of Dermatology, Centro Dermatológico Dr. “Ladislao de la Pascua”, Mexico City, México
² Department of Dermato-Oncology, Centro Dermatológico Dr. “Ladislao de la Pascua”, Mexico City, Mexico
³ Department of Dermatopathology, Centro Dermatológico Dr. “Ladislao de la Pascua”, Mexico City, México

Case Presentation

A 46-year-old male with history of complete surgical excision of a well-differentiated cutaneous squamous cell carcinoma in the right preauricular area in 2018 visited the dermatology unit complaining of 3 growing pink nodular lesions on the scalp (Figure 1A). Dermoscopy revealed multiple rosettes with homogeneous white-pink areas (Figure 1B). Two tumors were excised with a preliminary diagnosis of basal cell carcinoma, and histopathology reported molluscum contagiosum (MC) (Figure 1C). As the presence of giant MC on the face is a clue for HIV infection, laboratory tests were performed and confirmed the suspected cause of immunosuppression.

Teaching Point

The diagnosis of MC is straightforward when typical findings are seen; however, some cases may be indistinguishable from other tumors, such as basal cell carcinoma [1]. Dermoscopy can improve the accuracy of pink tumor diagnosis, as rosettes can be observed in many tumoral skin lesions [2]. Multiple pink nodular lesions on the face or scalp with rosettes on dermoscopy should raise the suspicion for MC.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.
References


Basal Cell Carcinoma Disguised Among Intradermal Nevi

Gabriel Salerni¹,²

¹ Dermatology Department, Hospital Provincial del Centenario de Rosario - Universidad Nacional de Rosario, Argentina
² Oroño Medical Diagnosis, Rosario, Argentina

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Corresponding author: Gabriel Salerni, MD, PhD, Dermatology Department, Hospital Provincial del Centenario de Rosario - Universidad Nacional de Rosario, Argentina; Oroño Medical Diagnosis, Rosario, Argentina. E-mail: gabrielsalerni@hotmail.com

Case Presentation

A 61-year-old woman presented to consultation for routine skin examination. Cutaneous examination revealed multiple longstanding firms, achromic, dome-shaped, papules, ranging from 5 mm to 12 mm in diameter (Figure 1A) located on the forehead. The patient was unaware of any change. Dermoscopy revealed remnants of light brown pigmentation, terminal hairs, comma-like (linear curved) vessels and comedo-like openings in lesions a to e (Figure 1B) which were suggestive of intradermal nevi. Lesion f displayed dermoscopic criteria for basal cell carcinoma consisting of a pink background, arborizing telangiectasias, gray-brown dots, and structureless areas.

Teaching Point

Dermoscopy improves the diagnosis of non-pigmented skin tumors because it allows the visualization of vascular patterns and residual pigmentation that are not visible to the naked eye [1,2]. In this case, dermoscopy provided crucial information for recognition of a basal cell carcinoma that might have been overlooked among multiple benign melanocytic lesions assessed solely by the naked eye.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.
Figure 1. (A) Multiple firms, achromatic, dome-shaped papules, located on the forehead. (B) Dermoscopy revealed criteria for intradermal nevi in lesions a to e, while lesion f displayed pink background, arborizing telangiectasias (arrows), gray-brown dots (circle), and structureless areas (asterisks) consistent with basal cell carcinoma.

References


Not Every Isolated Plantar Lesion Is a Wart: A Case of Pagetoid Reticulosis Presenting as an Acral Lesion

Leonel Hidalgo¹, Miguel Villaseca-Hernández¹,², Cristián Navarrete-Dechent¹,³, Álvaro Abarzúa-Araya¹,³

¹ Department of Dermatology, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
² Department of Pathology, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
³ Melanoma and Skin Cancer Unit, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Case Presentation

A 52-year-old woman was referred for a plantar wart. She reported a 2-month asymptomatic lesion on the right foot (Figure 1, A and B). Based on examination, surgery was performed to rule-out a malignant neoplasm. The histopathological features and immunostaining were consistent with pagetoid reticulosis (PR) (Figure 1, C and D).

Teaching Point

PR is a rare variant of mycosis fungoides, manifesting as solitary indolent scaly or verrucous plaque frequently misdiagnosed as dermatitis or psoriasis [1]. Dermoscopy provides diagnostic clues: plantar warts show disruption of dermatoglyphics and irregular capillaries due to weight bearing and trauma; calluses demonstrate homogenous opacities; corns exhibit a translucent core; Bowen disease has scale and glomerular vessels in clusters [2]. In this case dermoscopy showed a white hyperkeratotic center, aligned red dots, and slight-pinkish background. Prior reports of PR described regular dotted and glomerular vessels in a pinkish background, vessels halos, and scales [1].

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.
Figure 1. (A) Reticuloid pagetosis. A 1-cm skin colored hyperkeratotic papule in the lateral surface of the right foot. (B) Reticuloid pagetosis. Dermoscopy revealed a white hyperkeratotic center surrounded by aligned red dots amidst a slight-pinkish background (polarized dermoscopy, x10). (C) Reticuloid pagetosis. Photomicrograph showing hyperkeratosis and atypical lymphocytes with intense epidermotropism (H&E x 40). (D) Reticuloid pagetosis. Immunostain were positive for CD3, CD4, and CD8.

References


**A Gray Patient**

Gabriela Fortes Escobar¹, Kelli Wagner Gomes², Mariana Quirino Tubone³, Gabriela Maldonado⁴

1 Department of Dermatology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil  
2 Private Practice - Rua Felipe Camarão 690/Sala 402, Porto Alegre, Brasil  
3 Private Practice - Av. Marcolino Martins Cabral, 2099/ Sala 902, Tubarão, Brasil  
4 Private Practice - Rua 24 de Outubro, 1440/Sala 1103, Porto Alegre, Brasil

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Corresponding author: Gabriela Fortes Escobar, MD MSc Department of Dermatology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brasil. E-mail: gescobar@hcpa.edu.br

**Case Presentation**

A 46-year-old Caucasian woman presented with a 10-year history of an asymptomatic progressive darkening of the skin. There was no previous history of inflammation, and she denied the use of medications. Examination revealed symmetric blue-gray patches involving the face, trunk (Figure 1, A and B) and extremities. Dermoscopy showed a diffuse reticulated-homogenous brown-gray pigmentation (Figure 1C). Skin biopsy revealed multiple spindle-shaped dendritic melanocytes in the dermis (Figure 1D) and immunohistochemical staining was positive for Melan-A and HMB-45.

**Teaching Point**

Acquired dermal melanocytosis is a rare pigmentary disorder and its etiology remains unknown. Three theories may explain this disorder: migration of epidermal melanocytes to the dermis; migration of hair bulb melanocytes; or reactivation of pre-existing latent dermal melanocytes triggered by local inflammation or an unknown stimulus [1,2]. Melanin-containing dendritic melanocytes can be seen in the upper-middle portions of the dermis and, with the Tyndall effect, they result in a brown to bluish-gray skin pigmentation [2].

**Informed consent:** Written informed consent for publication of clinical details and clinical images was obtained from the patient.
Figure 1. (A) and (B) Remarkable blue-gray pigmentation on the trunk. (C) Dermoscopy (10x) revealing a diffuse reticulated-homogenous brown-gray pigmentation. (D) Histopathology showing multiple spindle-shaped dendritic melanocytes in the dermis (arrows).

References


Combined Epidermal-Follicular Mucinous Nevus: Dermoscopic Appearance

Arturo Robles-Tenorio¹, Francisco Javier Salazar-Torres¹

¹Dermatology Institute of Jalisco, “Dr. José Barba Rubio”, Zapopan, México


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Corresponding author: Robles-Tenorio, MD, MSc, Dermatology Institute of Jalisco, “Dr. José Barba Rubio”, Zapopan, México. E-mail: arturo.robten@gmail.com

Case Presentation

A 17-year-old Hispanic male presented with long-standing asymptomatic papules grouped as an irregular, brown, 10 cm × 6 cm × 0.2 cm plaque over the right aspect of the neck (Figure 1A). Perifollicular hypopigmentation and geometric brown structures were observed on dermoscopy (Figure 1B). Epidermal hyperkeratosis, acanthosis, papillomatosis, as well as abundant mucin deposits around the hair follicles were noted on histopathology, compatible with combined epidermal-follicular mucinous nevus (MN).

Figure 1. Combined epidermal-follicular mucinous nevus. (A) Clinical appearance. (B) Perifollicular hypopigmentation and pigmented geometric structures around the papules can be observed on dermoscopy.
Teaching Point

There are less than 30 reports of MN in the literature [1]. Histopathology is essential for the diagnosis, wherein mucin deposits along the superficial dermis are present. The combined epidermal subtype also exhibits hyperkeratosis, acanthosis, and rete ridges elongation. Perifollicular mucinous involvement has only been described in one case, yet epidermal changes were subtle [2]. In contrast, we observed epidermal changes and perifollicular mucin deposits, which correlated with perifollicular hypopigmentation observed in dermoscopy. The dermoscopic appearance of MN has not been previously documented.

Informed consent: Informed consent for publication of clinical details and clinical images was obtained from the patient.

References

Dermatofibrosarcoma Protuberans: Experience at a Third-Level Referral Center

Stefano Caccavale¹, Adriana Martins Basso², Paola Vitiello¹, Andrea Ronchi³, Antonello Sica⁴, Pasquale Verolino⁵, Ruzica Jurakic Toncic⁶, Giuseppe Argenziano¹

¹Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Naples, Italy
²Medicina Integrada, private practice, Sao Paulo, Brasil
³Pathology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Naples, Italy
⁴Oncology and Hematology Unit, Department of Precision Medicine, University of Campania “Luigi Vanvitelli”, Naples, Italy
⁵Plastic Surgery Unit, Multidisciplinary Department of Medical-Surgical and Dental Specialties, University of Campania Luigi Vanvitelli, Naples, Italy
⁶Department of Dermatology and Venereology, University of Zagreb, Zagreb, Croatia

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Corresponding author: Stefano Caccavale, MD, Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania Luigi Vanvitelli, Naples, Italy. Email: stefano85med@libero.it

Dermatofibrosarcoma protuberans (DFSP) is a soft tissue sarcoma, a rare and locally aggressive dermal and subcutaneous mesenchymal tumor. DFSP results frequently from the translocation t (17;22) with consequent fusion of the genes of collagen 1A1 (COLL1A1) and of platelet-derived growth factors B (PDGFB) that activate the signaling of tyrosine kinase [1]. DFSP is usually observed between the third and fourth decades of life. The distribution between sexes is similar, with a slight predominance in females [2]. DFSP typically presents as a slow-growing, reddish-brown plaque, with protruding firm smooth nodules (Figure 1). The most common sites are the trunk and proximal extremities. Usually, it is asymptomatic, being less commonly painful. Immunohistochemical staining is characteristically CD34-positive and factor XIIIa negative. Histopathologic features include a dense dermal tumor, the fascicles of which are interspersed with a storiform configuration, extending to the adipose tissue. Neoplastic cells are monomorphous and have hyperchromatic nuclei [3] (Figure 2).

The treatment is surgical with a clear histological margin. However, the recurrence rate is around 7.3% for excision with a margin of 2-4 cm. DFSP has low metastatic potential (2-5%) but a high rate of local recurrence after surgical excision. Mohs surgery reduces the recurrence rate (about 1%). Adjuvant radiotherapy can aid in reducing the local recurrence rate [1,3-5]). The use of imatinib reduces the size of
inoperable tumors. Follow-up visits are recommended every 3-6 months during the first 3 years [1].

An observational retrospective monocentric study was conducted. The patient list was extracted from the electronic database of the Dermatology Unit of the University of Campania Luigi Vanvitelli, Naples, Italy. Eligible cases affected by DFSP were identified in the retrospective search in the database in the period between January 2006 and November 2020. Cases lacking adequate clinical information (ie sex, age, anatomic site, histopathology) were excluded. We identified 29 cases with a clinical suspicion for DFSP (Table 1). Among them, 21 were confirmed by histological examination (10 men aged 23-68 years at the time of diagnosis, and 11 women 25-79 years old). We found a slightly higher prevalence in females (52.4%), in accordance with the literature. The mean age was 44 years for males and 47 years for females. The diagnosis of DFSP was only part of the clinical differential diagnosis in 8 patients (Table 2); the most frequent histological diagnoses in these patients were dermatofibroma and basal cell carcinoma (25% each).

The 21 histologically proven cases of DFSP had involvement of the following body areas: scalp, chest and inframammary, over surgical scar, back, abdomen, upper limb, groin, lower limb, and foot (Table 1). Among these areas, the chest was the most frequently affected by the tumor (33.3%) followed by the back and abdomen (14.3%, each).

Six patients did not return after the first visit or after surgery. Some of them had already had a biopsy in another
hospital and came to us asking for a second opinion. Among the 13 cases that returned only once for the follow-up visit, 1 patient was also affected by a melanoma and another one returned for management of urticaria. Only 1 patient underwent follow-up controls for more than 5 years.

The number of DFSP diagnosed in our Dermatology Unit between January 2006 and November 2020 is certainly not high, especially when compared to the huge number of patients that we see every day in our third-level referral center. Only 1 patient underwent follow-up controls for more than 5 years.

Table 1. Body Areas Affected by DFSP in Histologically Proven Cases

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Female</th>
<th>Age</th>
<th>Male</th>
<th>Age</th>
<th>Number of Cases for Each Body Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologically proven cases of DFSP</td>
<td>21</td>
<td>11</td>
<td>25-79</td>
<td>10</td>
<td>23-68</td>
</tr>
<tr>
<td>Clinical suspicion of DFSP</td>
<td>29 (21 confirmed with HPE)</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical suspicion of DFSP not confirmed with histopathology</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DFSP = dermatofibrosarcoma protuberans; HPE = histopathologic examination.

Table 2. Patients With Clinical Suspicion of DFSP and Their “True” Diagnoses After Histopathologic Examination

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Number of Patients for Each Histopathologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical suspicion of DFSP</td>
<td>2 dermatofibroma</td>
</tr>
<tr>
<td>Clinical suspicion of DFSP not confirmed with histopathology</td>
<td>2 basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>1 invasive melanoma</td>
</tr>
<tr>
<td></td>
<td>1 squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>1 hypertrophic scar</td>
</tr>
<tr>
<td></td>
<td>1 trichilemmal cyst</td>
</tr>
</tbody>
</table>

DFSP = dermatofibrosarcoma protuberans; HPE = histopathologic examination.

References


Atopic Dermatitis Pathogenesis: Lessons From Immunology

Luis F Santamaria-Babí¹

¹Translational Immunology, Department of Cellular Biology, Physiology and Immunology, Faculty of Biology, University of Barcelona, Parc Científic de Barcelona, Barcelona, Spain

Key words: atopic dermatitis, translational research, homing, CLA

Abbreviations: CLA: Cutaneous Lymphocyte-Associated Antigen; Sa: Staphylococcus aureus; AD: atopic dermatitis

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Corresponding author: Luis F Santamaria-Babí, PhD, Professor of Clinical and Translational Immunology. Translational Immunology. Parc Científic de Barcelona, Barcelona, Spain. E-mail: Luis.santamaria@ub.edu

Translational research has changed the understanding of atopic dermatitis (AD) pathogenesis beyond the basic mechanisms of immunology. The study in patients of rational therapies based on targeted therapies (biologics) provides valuable information from the patient and provides lessons of clinical immunology on clinically relevant mechanism of AD pathogenesis. AD features such as skin barrier defect, skin dysbiosis, and pruritus share a common abnormal adaptive immune response process. Skin-homing CLA+CD4+ memory T-cells produce IL-4, IL-13, and IL-31 which are key mediators in AD pathogenesis. Lessons learned from AD show that translational immunology allows generating rational therapies for AD and learning its immunopathogenesis in the patient.
Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a defective epidermal barrier, cutaneous dysbiosis, pruritus, in a context of abnormal immune response [1]. The translational research model, originally applied to plaque psoriasis, has revolutionized the concepts of moderate to severe AD pathogenesis and has provided relevant clinical information on the important immunological mechanisms of AD [2]. Translational research allows validating in the patient new pathological mechanisms proposed in basic research. The use of targeted therapies such as humanized monoclonal antibodies directed to human targets (cytokines, receptors, cells…) in clinical trials, together with advanced technologies analyzing molecular mechanisms in patients (transcriptomics, proteomics…), has demonstrated that AD is a complex and heterogeneous condition that can now be treated more effectively with rational therapies directed to the pathogenic basis of the disease. The “omics” revolution facilitated the understanding of AD pathogenesis at molecular level beyond clinical scores. Now all clinical studies with innovative drug therapies incorporate this molecular phenotyping of patients [3]. This review highlights, from a translational immunology perspective, recently identified immunological mechanisms involved in moderate to severe AD pathogenesis that are clinically relevant (Table 1).

Type 2 (T2) Immune Response in AD

Many AD patients exhibit an exaggerated immune T2 response that leads to increased IgE levels. The T2 immune response consists of the production of IL-4, IL-13, and IL-5 by memory CD4+ Th2 cells, type-2 innate lymphoid cells (ILC2), mast cells, and basophils [4]. Thus, T2 immune response includes adaptive and innate mechanisms. The adaptive response is based on the capture of allergens, antigens, and superantigens by antigen presenting cells and presentation to specific CD4 memory T-cells that are activated and secrete IL-13, IL-4, IL-31, and IL-22 (Figure 1). On the other hand, the innate response is based on ILC2 cells that are tissue-resident and produce IL-5 and IL-13. To secrete cytokines, ILC2 lymphocytes need to be activated by epithelial cytokines, also termed alarmins, produced by keratinocytes. The best characterized alarmins are TSLP (thymic stromal lymphopoietin), IL-25, IL-33, and IL-1α [1]. They have been very well studied also in AD [5,6].

Th2 Response and Translational Research in AD

IL-13 and IL-4 have been demonstrated to be clinically relevant in AD by targeted therapeutic strategies since neutralization of IL-4Rα and IL-13 clearly improved AD by inhibiting IL4/IL-13 and IL-13 biological activities, respectively [7]. In recent years, several clinical trials with biological therapies have sought to explore the relevance of Thymic stromal lymphopoietin (TSLP), IL-25, IL-33 as possible new therapeutic targets for AD since they induce T2 response in ILC2. Lessons from these clinical trials that explore the roles of those alarmins in AD patients indicate that the neutralization of TSLP, IL-25 and IL-33 is not effective in improving disease [8]. In contrast to AD, in asthma the clinical importance of IL-33 and TSLP is well demonstrated [9]. Since T2 cytokines can also be produced by CD4+ memory T-cells, at the present time, clinical efficacy in patients supports more strongly the relevance of the adaptive immune response in contrast to the innate response. In fact, CD4+ memory Th2 cells are the most abundant in inflamed lesions and considered the most important [1]. Interestingly, blockage of antigen presentation to

Table 1. Targeted Therapies in Moderate-to-Severe Atopic Dermatitis.

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism</th>
<th>Therapy</th>
<th>Clinical evidence in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4RA</td>
<td>IL-4, IL-13</td>
<td>Anti-IL-4RA</td>
<td>+</td>
</tr>
<tr>
<td>IL-13</td>
<td>IL-13</td>
<td>Anti-IL-13</td>
<td>+</td>
</tr>
<tr>
<td>IL-31</td>
<td>IL-31</td>
<td>Anti-IL-31RA</td>
<td>+</td>
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<tr>
<td>IL-22</td>
<td>IL-22</td>
<td>Anti-IL-22</td>
<td>+</td>
</tr>
<tr>
<td>OX40L</td>
<td>Antigen presentation</td>
<td>Anti-OX40L</td>
<td>+</td>
</tr>
<tr>
<td>CCR4</td>
<td>CCR4 mediated CLA+ T-cell chemotaxis by CCL17 and CCL22</td>
<td>CCR4 antagonist small molecule</td>
<td>+</td>
</tr>
<tr>
<td>IL-17A</td>
<td>IL-17A</td>
<td>Anti-IL-17A</td>
<td>-</td>
</tr>
<tr>
<td>IL-5</td>
<td>Eosinophil biology</td>
<td>Anti-IL-5</td>
<td>-</td>
</tr>
<tr>
<td>TSLP</td>
<td>Innate T2 response. TSLP activation of ILC2</td>
<td>Anti-TSLP</td>
<td>-</td>
</tr>
<tr>
<td>IL-33</td>
<td>Innate T2 response. IL-33 activation of ILC2</td>
<td>Anti-IL-33</td>
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<tr>
<td>IL-25</td>
<td>Innate T2 response. IL-25 activation of ILC2</td>
<td>Anti-IL-25</td>
<td>-</td>
</tr>
<tr>
<td>IL-23</td>
<td>IL-23/Th17 axis</td>
<td>Anti-IL-23p19</td>
<td>-</td>
</tr>
</tbody>
</table>

TSLP = Thymic stromal lymphopoietin.
CD4+ memory T-cells by a humanized monoclonal antibody that inhibits the OX-OX40L interaction has demonstrated to be effective in the clinic (Figure 1) [10]. IL-5 constitutes another T2 cytokine that regulates eosinophil generation and survival. In AD, neutralization of IL-5 has not provided clinical improvement in patients, whereas in asthma, it constitutes a biological therapy already approved [8].

**Novel Insights on IL-13 Relevance in AD**

IL-4 and IL-13 represent the best clinically validated cytokines in AD due to the efficacy of biologicals targeting IL-4RA and IL-13. Recent studies in AD lesional skin indicate that IL-13 may have more relevance in the inflammatory processes that take place in the skin than IL-4 [7]. IL-13 receptors, IL-13RA1 and IL-13RA2, are preferentially found in non-hematopoietic cells such as keratinocytes and fibroblasts. In addition, IL-13 is expressed in higher level in AD lesions compared to IL-4, and transcriptomic analyses have demonstrated a dominant IL-13 molecular signature [11]. Interestingly, JAK1 is the most highly expressed member of the JAK family in lesional AD biopsies and is involved in IL-13 signal transduction [12]. Besides this, IL-13 also plays a relevant role in the recruitment of pathogenic skin-homing memory T-cells that express the cutaneous lymphocyte-associated antigen (CLA) positive on their surface [1,13]. IL-13 and CCR4 are closely related in AD inflammation. The CCR4 is a chemokine receptor preferentially expressed by CLA+CD4+ T-cells [14] whose ligands are CCL17 and CCL22 and are induced in keratinocytes upon IL-13 activation and preferentially attract CLA+CD4+ lymphocytes [15]. Interestingly, CCL17 is considered a relevant biomarker for AD [16] and a recent study has shown that a small molecule antagonist of the CCR4 receptor can improve AD [17].

**IL-13 and IL-4 Affect the Skin Barrier Function and the Microbial Cutaneous Colonization by Staphylococcus aureus in AD**

The skin barrier integrity is damaged in AD cutaneous lesions making the stratum corneum permeable to allergens, microbes, and their toxins. Besides genetic structural defects, such as filaggrin mutations, which are present in some AD patients, IL-13 and IL-4 reduce the expression of relevant skin elements involved in the skin barrier such as filaggrin, loricrin, involucrin and important lipid components [18,19]. By far, *Staphylococcus aureus* (Sa) is the best characterized microorganism in AD because it is present on the skin of AD patients [20]. In fact, Sa skin-colonized AD patients have been recently shown to present a more severe form of disease than...
non-colonized ones [21]. Th2 cytokines have been shown to facilitate skin colonization by Sa since they reduce the expression of natural antimicrobial peptides, thus reducing defenses against Sa infection, favoring Sa skin adherence by promoting fibronectin production [20].

**Immunological Mechanisms of Pruritus**

Itch is probably the symptom that most affects the quality of life of AD patients, and it is part of the itch-scratching cycle that most patients suffer from [22]. The adaptive immune response is responsible to a great extent of the pruritus present in AD as demonstrated by biological therapies and small molecules that inhibit key signaling pathways involved in pruritus. There are 2 different immunological mechanisms behind the adaptive immune response and signal transduction of itch by sensitive nervous fibers in the skin. CD4+ Th2 cells producing IL-4 and IL-13, and the Th2 related IL-31. These 3 cytokines stimulate sensitive cutaneous fibers that express their specific receptors to transmit pruritus to the central nervous system through JAK1 kinase signaling [23]. The relevance of IL-4 and IL-13 in pruritus is supported by the important release of itch by neutralizing antibodies to IL-4RA and IL-13 in moderate to severe patients. In addition, small molecules that act as JAK inhibitors and block JAK1 signaling of IL-4 and IL-13 receptors, are also potent therapies that act on immune-mediated itch. IL-31 is a unique cytokine since it is mainly involved in pruritus generation. CLA+CD4+ memory T-cells constitute the main source of IL-31 [24]. IL-31 binds to the IL-31RA that it is expressed in cutaneous sensitive neurons and transduces signaling through JAK1 signaling. The relevance of IL-31 in itch in AD patients is supported by the antipruritic activity of anti-IL-31RA which is currently in phase III trials [25].

**Immunological Response In AD: Beyond Th2 and Th1**

The classical model of AD pathogenesis where the acute phase is Th2 and the chronic stage is Th1 has evolved to more a complex scenario including Th1, Th2, Th17, and Th22 cytokines [26]. However, the presence of all those T-cell subtypes in AD does not imply they are clinically relevant players. At present, translational research has demonstrated that only some of them are important, although it cannot be discarded that in different AD phenotypes, endotypes, or ethnicities these cytokines may be relevant. IL-22, IL-17A and IL-23 are well characterized mediators of inflammation in psoriasis; however, they are also present in AD inflammation. The study of specific antibodies for these cytokines in AD patients has clarified their role in this disease. Neutralization of IL-22 improved AD preferentially in patients with increased lesional expression of IL-22 at baseline [27]. Current efforts to demonstrate the clinical relevance of IL-17A and IL-23 have failed since neutralization of those cytokines in patients has not provided any clinical benefit [8]. In relation to the immune response, new technologies in simultaneous quantification of serum biomarkers of immune response have allowed to classify moderate to severe AD patients into 4 endotypes which demonstrate patients heterogeneity. These are IL-1R1 and skin-homing tropism, dominant Th1/Th2/Th17 response, Th2/Th22/CCL18 response, and low levels of Th2 cytokines and eosinophilia [28].

**Circulating CLA+ Memory T Cells and AD**

Circulating T-cells expressing the CLA antigen represent a subset of memory T-cells that reflect cutaneous immunological abnormalities taking place in the skin [29]. They are used to understand atopic dermatitis phenotypes as possible cell biomarkers of disease [30,31]. The translational relevance of this subset in AD, which also exists in human circulation as resident memory Th2 cells, as well as in the skin [32], has been further studied during dupilumab treatment of moderate to severe AD patients. At week 4 of treatment, dupilumab decreased IL-4, IL-13 and IL-22 production in CLA+CD4+CCL18, but not in the CLA- memory T cells subset [33,34]. These results indicate that circulating skin homing lymphocytes preferentially respond to IL4RA blockage in AD patients and are in line with the relevance of adaptive immune response in AD in the current model of AD [1].

**Conclusions**

Current translational immunology results support a simplified model of AD pathogenesis (Figure 1), where patients carry an abnormal immune response that reacts to agents accessing the skin trough a permeable skin barrier, in the context of the itch-scratching circle. Circulating CLA+CD4+CCL18 memory T-cells infiltrate non-lesional skin and become activated by antigen presenting cells and secrete IL-4, IL-13, and IL-31 among other cytokines. IL-4 and IL-13, and in particular IL-13 due to the presence of the IL-13 receptor in the skin and greater amount of IL-13 than IL-4, alter skin barrier function. In addition, IL-13 would promote Sa colonization by decreasing natural antimicrobial peptides and adherence through increased production of fibronectin. Those 3 cytokines mediate pruritus by binding to their specific receptors in sensitive neurons that transmit pruritus to central nervous system. IL-13 would promote inflammation by the recruitment of skin-homing CLA+CD4+CCL18 that are attracted by IL-13-activated keratinocytes that produce CCL17.
References


Atopic dermatitis is a Th2 disease, due to relapse of IL-4 and IL-13 by Th2 cells. Despite the approval by FDA of dupilumab, the first monoclonal antibody for the severe forms, traditional drugs remain a milestone for the treatment of this dermatosis. Dermatologists need a good knowledge of all therapies for an integrated and personalized management of patients.
Conventional treatments represent a cornerstone of AD therapy and are the first-line therapy for the mild-moderate forms. With biological drugs rapidly emerging, it is important for clinicians to combine the new treatments with the traditional ones to improve the response of the patients [1-4,17].

**Conventional therapy for AD**

Conventional treatments for AD can be differentiated in topical and systemic. Topical agents are moisturizers, corticosteroids, calcineurin inhibitors and antimicrobials/anti-septics, used in monotherapy or in combination. In the field of topical therapies, wet wrap therapy must also be mentioned [5-9].

Systemic treatments, used for severe and recalcitrant forms, consist in phototherapy, systemic corticosteroids, cyclosporine, methotrexate, mycophenylate mofetil and azathoprine [10].

**Moisturizers**

Moisturizers are used to combat xerosis (one of the cardinal clinical features of AD and the result of a dysfunctional epidermal barrier) and transepidermal water loss. They reduce disease severity, the need for pharmacologic intervention and should be applied soon after bathing, almost once a day [5-7].

Moisturizers can be classified in traditional (glycol and glyceryl stearate, soy sterols, petrolatum, dimethicone, mineral oil, glycerol, lactic acid, urea) and prescription emollient devices (PEDs). Traditional agents contain varying amounts of emollient, occlusive and humectant ingredients. Emollients (eg glycol and glyceryl stearate, soy sterols) lubricate and soften the skin, occlusive agents (eg petrolatum, dimethicone, mineral oil) form a layer to reduce evaporation of water, while humectants (eg glycerol, lactic acid, urea) attract and hold water. Several clinical trials have shown that they lessen symptoms and signs of AD, including pruritus, erythema, fissuring, and lichenification [5-7].

The term PED has been introduced to identify a new class of topical agents designed to target the specific defects in skin barrier function observed in AD. They include preparations having distinct ratios of lipids that mimic endogenous compositions and containing palmitoylthanolam ide, glycyrrhetinic acid, or other hydrolipids. PEDs may contain an antioxidant agent, such as furfuryl palmitate or furfuryl derivatives. PEDs lessen xerosis and inflammation but they have been tested in a small number of controlled studies [11].

Moisturizers are the main primary treatment for mild forms and should be part of the regimen for moderate and severe ones because they reduce inflammation, the prescription of topical corticosteroids and prevent the flares in the maintenance treatment. There are few studies that have compared moisturizers, but results are overlapping. Therefore, the choice of moisturizing agent is highly dependent on individual preference [5].

In AD, the alteration of skin barrier is associated with reduced ceramide levels, with a consequential increase in transepidermal water loss (TEWL) and reduction in skin hydration.

It is not yet known whether dupilumab restores skin barrier function. The latter can be investigated using TEWL (that is the water vaporization rate in g/h/m²) and stratum corneum hydration (SCH) (the water content in the stratum corneum measured by Corneometer®).

According to a recent study, following treatment with dupilumab, TEWL decreases quickly in the skin interested by AD, while SCH does not improve. Because of the small sample size in this study, further papers are needed but it seems that dupilumab have no effects for dry skin conditions and patients have to continue the use of moisturizers [12].

**Topical corticosteroids**

Topical corticosteroids (TCS) inhibit the antigen processing and suppress the release of pro-inflammatory cytokines, acting on a variety of immune cells, including T lymphocytes, monocytes, macrophages, and dendritic cells. Their efficacy has been demonstrated, with more than 110 different randomized controlled trials [5]. Twice daily application of corticosteroids is generally recommended for the treatment of AD; however, evidence suggests that once daily application may be sufficient. As maintenance therapy to reduce the number of relapses, a “proactive” approach can be prescribed. It consists of applying TCS intermittently once or twice a week in the areas most prone to relapse, even when no inflammatory lesions are visible. The CHRONOS study examined the use of dupilumab combined with topical corticosteroids versus placebo in 52 weeks of treatment. Thanks to the combination with topical corticosteroids, 10% of patients more than in the SOLO studies (that have tested just dupilumab versus placebo) achieved a 75% reduction in EASI score [13].

**Wet Wrap Therapy**

The wet wrap therapy (WWT) is a method to quickly reduce AD severity, used for significant flares and recalcitrant disease. It consists in the application of topical agent (TCS or moisturizers or combination of both) covered by a wetted first layer of tubular bandages, gauze, or a cotton suit, followed by a second dry layer.

WWT increases the penetration of topical therapy and reduces the water loss. The wrap can be worn from several hours to 24 hours at a time, depending on patient tolerance.
and the application can be repeated for several days up to 2 weeks. The major limitation of this technique is represented by the lack of practicality and the low tolerance for patients, especially if children [8,9].

**Topical Calcineurin Inhibitors**

Topical calcineurin inhibitors (TCIs) inhibit calcineurin-dependent T-cell activation, blocking the production of pro-inflammatory cytokines. Two types of TCIs are available: tacrolimus ointment (0.03% and 0.1% strengths) and pimecrolimus cream (1% strength). TCIs are recommended and effective for acute and chronic treatment, twice a day, as well as maintenance, in both adults and children with AD. They can be used as steroid-sparing agents in long term therapy because they do not cause cutaneous atrophy and can be used in sensitive areas, such as the face, skin folds and genitals. Tacrolimus 0.03% ointment and pimecrolimus cream are indicated for use in individuals aged 2 years and older, while tacrolimus 0.1% strength is only approved in those over age 15 years. Proactive, intermittent use of TCIs as maintenance therapy (2–3 times a week) on areas that commonly flare is recommended to prevent relapses and is more effective than the use of emollients alone. This strategy has been tested for up to 1 year, without significant adverse events. The most common side effects are local reactions such as stinging and burning. TCIs may be combined with TCS [5].

For patients undergoing dupilumab injections, tacrolimus ointment and pimecrolimus cream may be helpful to treat facial eczema (that responds later to dupilumab) and peripalpebral dermatitis (as a prevention of dupilumab associated conjunctivitis). Conjunctivitis is the most common side effect of dupilumab [14]. The prescription of trehalose/hyaluroate tear substitute and the treatment of peripalpebral and facial eczema with topical therapy reduce the incidence of dupilumab-associated conjunctivitis (incidence equal to 5% with preventive therapy versus an incidence of 8% and 8-23% without preventive therapy, according to trial studies and real life studies respectively) [15]. Moreover, new emerging problems are reported in literature: recalcitrant (pre-existing biological therapy) and dupilumab-associated (probably induced by biological therapy) face and neck dermatitis are described and can benefit by topical therapy (antifungal-corticosteroids and tacrolimus ointment). Various etiopathogenic mechanisms for these new regional dermatoses have been proposed but more studies are needed [16].

**Phototherapy**

Phototherapy is used as second-line treatment, after failure of first-line treatment (emollients, topical steroids, and TCIs), or as maintenance therapy in patients with chronic disease. Multiple forms of light therapy are beneficial for disease and symptom control, including: natural sunlight, narrowband (NB) UVB, BB-UVB, UVA, topical and systemic PUVA. Home phototherapy under the direction of a physician may be considered for patients who are unable to receive phototherapy in a medical office setting.

The light modality chosen should be guided by factors such as availability, cost, patient skin type, skin cancer history, and patient use of photosensitizing medications (for example calcineurine inhibitor). The dosing and scheduling of light should be based on minimal erythema dose and Fitzpatrick skin type. Phototherapy is usually administered 3 times a week.

NB-UVB is generally the most commonly recommended light treatment, considering its low risk profile and the relative efficacy. Several common adverse effects include: actinic damage, local erythema and tenderness, pruritus and burning [10].

**Systemic Corticosteroids**

The management of AD with systemic corticosteroids should generally be avoided because of short- and long-term adverse effects. Their use should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy [10].

**Cyclosporine**

Cyclosporine (CSA) is an immunosuppressant of T-cells and interleukin-2 production, used for adult and pediatric patients with severe or refractory form of AD. The dosage of CSA (available in oral capsules and solution) ranges from 3 to 6 mg/kg/d, standardly 150 to 300 mg/day in adults, divided in two doses. The initial and maintenance dose of CSA should be based on multiple factors, including the patient’s disease severity and other medical morbidities. Potential adverse effects include: hypertension, infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma. Thus, patients receiving CSA should be monitored for such potential consequences. The recommended time limit for consecutive use of CSA is currently 1 year. Before starting therapy, the following tests should be prescribed: blood count, renal and liver function, lipids, electrolytes, uric acid, hepatitis B and C markers, HIV and human chorionic gonadotropin (HCG) if indicated. During therapy, blood pressure should be measured twice a week and blood tests should be tested monthly [10]. CSA can be associated with dupilumab in the initial phase of therapy to induce faster the clinical remission or in patients recalcitrant to dupilumab in monotherapy [17].
**Methotrexate**

Methotrexate (MTX) is an antifolate metabolite and blocks the synthesis of DNA, RNA, and purines. It is also thought to negatively affect T-cell function. Its many off-label uses include treatment of refractory AD. MTX is available in solution (for intramuscular or subcutaneous injection) and oral tablet form. MTX is usually given as a single weekly dose. The dose range for MTX in patients with AD is extrapolated from its use in psoriasis and it is between 7.5 and 25 mg weekly. Folate supplementation is recommended during treatment with MTX. Nausea and other gastrointestinal symptoms may preclude oral administration. Severe adverse effects, including bone-marrow suppression and pulmonary fibrosis, can occur. Literature suggests that bone-marrow suppression is often reversible upon MTX dose reduction or discontinuation. Risk for skin cancer and lymphoma has been reported, although some cases of lymphoma arising during low-dose treatment have regressed on drug discontinuation. Pulmonary fibrosis may occur with short- or long-term use of the medication, such that patients with pulmonary diseases (eg asthma, chronic cough) may not be candidates. Before starting therapy, the following tests should be prescribed: blood count, renal and liver function, lipids, electrolyte, uric acid, hepatitis B and C markers, HIV and HCG if indicated. During the therapy, blood tests should be tested monthly. There are no data about use of MTX in children affected by AD. Multiple studies regarding its use in pediatric patients with psoriasis show MTX as a safe, effective, and well-tolerated medication [10]. Like cCSA, MTX can be associated with dupilumab in recalcitrant patients, maintaining a good safety profile [17].

**Azathioprine**

Azathioprine (AZA) is a purine analog that inhibits DNA production, thus preferentially affecting cells with high proliferation rates, such as B-cells and T-cells during inflammatory disease states. It is used off-label to treat inflammatory cutaneous and systemic disorders, including refractory AD with moderate improvement of dermatitis (equal to a 37% reduction of disease, measured by the Six Area, Six Sign AD scoring system after 12 weeks) [18]. A delayed effect may be noted, with some patients needing a treatment for 12 weeks or longer to achieve full clinical benefit. The dose range is variable between 1 to 3 mg/kg/d. AZA is available in tablet form only and may be given once daily.

Graduated dosing to maximize benefit while limiting side effects is preferred, as a considerable number of patients develops intolerable nausea and vomiting at higher doses. The metabolism of AZA is dependent on an individual’s thiopurine S-methyltransferase (TPMT) activity level, a principal enzyme in the thiopurine pathway. Genetic polymorphisms in TPMT activity are linked to a patient’s susceptibility to AZA toxicity, such that the homozygous carrier state of low or absent enzyme capacity poses the greatest toxicity risk. Thus, baseline TPMT level testing is strongly recommended before AZA initiation, with avoidance of use in those with very low or absent enzyme activity. Concomitant phototherapy is not advised because of increased risk of DNA damage and possible photocarcinogenicity. Nausea, vomiting and other gastrointestinal symptoms (bloating, anorexia, cramping) are common adverse effects. Other side effects include headache, hypersensitivity reactions, elevated liver enzymes, and leukopenia. AZA can be used for pediatric population in case of recalcitrant dermatitis but there are not sufficient data to recommend an optimal dose, duration of therapy, or to predict the relapse rate upon discontinuation. However, the most common dosage given is 2.5 mg/kg/d, with a higher treatment range maximum of 4 mg/kg/d relative to adult dosing (maximum 3 mg/kg/d) [10].

**Mycophenolate Mofetil**

Mycophenolate mofetil (MMF) is an immunosuppressant that blocks the purine biosynthesis pathway of cells via the inhibition of inosine monophosphate dehydrogenase, selectively affecting B- and T-cells. It is recognized as an off-label therapy in patients with refractory forms of AD. Insufficient data exist to make recommendations regarding the optimal MMF dosing or duration of therapy for patients with AD. Dosing ranges from 0.5 to 3 g/d. MMF is available in oral suspension, capsules, and tablets, and it is given twice daily. MMF is generally well tolerated, with nausea, vomiting, and abdominal cramping being the most common side effects. Rarely, hematologic (anemia, leukopenia, thrombocytopenia) and genitourinary (urgency, frequency, dysuria) toxicities have been reported. There is a theoretical risk of increased susceptibility to viral and bacterial infections while taking MMF, as it is clearly observed in patients with organ transplantation. Cutaneous malignancy and lymphoma are potential risks [10].

**Conclusions**

The introduction of dupilumab has changed the management of patients with severe forms of AD but traditional drugs remain a milestone for the treatment of mild-moderate AD and for combined therapies. Therefore, dermatologists need a good knowledge of both fields of interest for an integrated and personalized management of patients.
Table 1. Key points

| Moisturizers | Integral part of AD therapy, including in patients on biological treatment since it is able to reduce inflammation and itching but not xerosis. |
| Topical corticosteroids | Recommended for mild-to-moderate forms; they can be also helpful to accelerate the response to systemic drugs, including biologics, to increase the efficacy and to control the flares. |
| Topical calcineurin inhibitors | Recommended as steroid-sparing agents in long term therapy and mostly for the sensitive areas (face, skin folds and genitals). Useful to treat facial dermatitis (not responsive to dupilumab or dupilumab associated) and to prevent dupilumab associated conjunctivitis, if peripalpebral eczema is present. |
| Phototherapy | Used as second-line treatment, after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors), or as maintenance therapy in patients with chronic disease. |
| Traditional systemic drugs | First line therapy for severe forms and a valid choice in combination with dupilumab and in case of inadequate response to biological drug, maintaining a good safety profile. |

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