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Dermoscopy for Acral Melanocytic Lesions: Revision of the 3-step Algorithm and Refined Definition of the Regular and Irregular Fibrillar Pattern

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Acral melanoma (AM) is the most prevalent subtype of malignant melanoma in non-white populations. It is often detected in advanced stages, resulting in poor prognosis. However, the prognosis is favorable if detected in the early stages; almost all the patients with AM in situ are cured only by surgical excision with a narrow margin. Thus, early detection is essential in the management of AM. Although clinical differentiation between early AM and acral nevus is sometimes very difficult, dermoscopy is highly helpful in the differentiation [1]. A commonly detected, specific dermoscopic pattern of early AM is the parallel ridge pattern (PRP), exhibiting band-like pigmentation on the surface ridges of the skin markings (dermatoglyphics) [2]. In contrast, the main dermoscopic pattern of acral nevus is the parallel furrow pattern (PFP) showing linear pigmentation along the sulci of the skin markings. Other dermoscopic patterns frequently observed in acral nevus are the lattice-like pattern and the fibrillar pattern (FP), both being modifications of the PFP [3].

The 3-step Algorithm and its Re-revision

Based on these characteristic dermoscopic findings, in 2007 our group proposed a dermoscopic 3-step algorithm for the management of acral melanocytic lesions [3] and then, revised it in 2011 [4]. Recently, several studies were reported which examined utility of the 3-step algorithm [5-7]. In these studies, the 3-step algorithm generally worked well, however, in one study, the algorithm missed one lesion of AM, 0.5 mm in Breslow thickness. The lesion, 6 mm in diameter, did not show the PRP but exhibited a multicomponent pattern. Considering rather lower sensitivity of the PRP in AM of their case series, Lallas et al proposed the BRAAFF checklist for the effective detection of AM, which included irregular blotch and asymmetry of structures and colors as positive features [8]. These findings along with our further experience prompted us to re-revise the 3-step algorithm as shown in Figure 1. This version includes a multicomponent...
pattern in the first step as well as a follow-up strategy after the third step.

One possible problem in using the 3-step algorithm is judgment of whether the FP is regular or irregular. According to Costello et al, physicians often did not recognize the regular FP as a benign pattern [6]. The FP is characterized by densely packed brownish fibrillar lines arranged in a parallel fashion and crossing the skin markings. Each fibril of the pattern corresponds to a melanin column in the thick cornified layer which is obliquely arranged due to the mechanical pressure from the body weight. This is the reason for the predilection of nevi of this pattern for the pressured areas of the sole [9]. Thus, the FP is regarded as an artifactual expression of the PFP [1, 3]. Noteworthy is that the FP is occasionally found focally within a lesion of AM [1]. This is not strange because, as mentioned above, the FP is detected in the pressured areas of the sole, which are the most prevalent subsite of AM. Moreover, the FP can occupy an almost entire lesion of AM in situ, particularly in its early evolving stages [10,11]. This could lead us to misdiagnosis of AM in situ as acral nevus. Hence, it is very important for us to correctly differentiate the FP of early AM in situ from that of acral nevus.

Criteria for Regular and Irregular Fibrillar Pattern and Clues to the Management

Herein, based on our experience, we refine the definitions of the “regular” and “irregular” FP, and then write down several clues which help us in the management of acral lesions showing the FP. The oblique dermoscopy [12] and the furrow ink test [13, 14] are very helpful in the evaluation of the FP.

Regular FP of acral nevus

The fibrils constituting the regular FP are evenly distributed throughout the lesion and mostly same in color and thickness (Figure 2A). The endpoints (deeper color ends) of the fibrils tend to line up on the sulci of the skin markings. In addition, not infrequently, the FP is combined with the PFP and/or changes to the PFP at the periphery. In most cases, the oblique dermoscopy demonstrates that the FP is originally the PFP (Figure 2B).

Irregular FP of acral melanoma

The fibrils constituting the irregular FP are unevenly distributed and variable in color and thickness (Figure 3). In most cases, the endpoints of the fibrils are arranged randomly.

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**Figure 1.** The re-revised 3-step algorithm for the management of melanocytic lesions on acral volar skin. The main targets of this algorithm are macular/patch lesions seen in adults. Apparently congenital lesions and nodular lesions are excluded from the evaluation.
In some lesions, however, they are located within the width of the ridges of the skin markings. Moreover, the PRP is not infrequently detected at least focally within a lesion. By the oblique dermoscopy, the irregular FP does not change to the PFP but, though rarely, to the PRP [10].

In addition to the aforementioned criteria, there are several findings which are helpful when we manage acral lesions showing the FP. They are summarized as follows.

1. If, in a lesion of the FP, non-site specific dermoscopic findings of melanoma (eg irregular streaks, irregular dots/globules, irregular blotches, blue-white veils, and/or regression structures) are detected, the lesion should be treated as AM.
2. Acral lesions exhibiting the negative fibrillar pattern should be biopsied for histopathologic evaluation (Figure 3). This pattern consists of whitish rods arranged in a parallel fashion on the dark structureless or fibrillar background [15]. The whitish rods represent intracorneal eccrine ducts. In our recent study of acral nevi (41 lesions) and AM in situ (10 lesions), the sensitivity and specificity of this finding for AM in situ were 40% and 90%, respectively [16].
3. A very early lesion of AM in situ could show the FP entirely composed of densely packed very thin fibrils crossing the surface ridges but uninvolving the sulci (Figure 4). This finding may be misinterpreted as the “regular” FP. But it does not change to the PFP on oblique dermoscopy. Such a lesion should be biopsied or carefully followed, particularly when seen in elderly persons. In our case series, this “regular” FP was observed in 2 out of 10 lesions of AM in situ showing the FP [16].
4. If the fibrils composing the FP is thick and regular in color, the lesion is certainly diagnosed as acral nevus, particularly when the lesion is small, ie, less than 5 mm in diameter (Figure 5).
5. When we cannot determine whether the FP is regular or irregular, periodic follow-up of the lesion is recommended, with a frequency of once or twice a year.

It is widely accepted that dermoscopy is quite helpful in the evaluation of pigmented lesions on acral volar skin. We believe the re-revised 3-step algorithm and refined criteria for the regular and irregular FP described in this commentary will further assist clinicians in managing acral melanocytic lesions appropriately, though their validity must be evaluated in larger case series.
Figure 3. Irregular fibrillar pattern of acral melanoma in situ. This lesion of the multicomponent pattern is mostly composed of fibrils and can be regarded as the irregular FP by our definition, ie, the fibrils constituting the pattern are irregular in color, thickness and distribution, and their endpoints do not line up on the sulci of the skin markings. (A) Transition to the parallel ridge pattern is detected in the right lower portion. The negative fibrillar pattern (whitish rods arranged in a parallel fashion) are detected in the left area, which is well recognized in (B), an image of higher magnification corresponding to the square area in (A). (B) Arrows indicate some of the whitish rods.

Figure 4. “Regular” fibrillar pattern seen in acral melanoma in situ (A, inset: clinical features: a brown patch, 13.5 × 10.5 mm in size, seen on the sole of a 78-year-old woman). (A) The very thin fibrils constituting this fibrillar pattern are evenly arranged and regular in color and thickness. (B) the square area in (A). The furrow ink test reveals that the sulci of the skin markings, indicated with arrows, are spared from the fibrillar pigmentation. (C, D) Histopathological features. (D) corresponds to the square area in (C). The thick cornified layer is obliquely arranged, as indicated with arrows in (C). The increased number of melanocytes are mainly detected in the crista profunda intermedia indicated with asterisks in (C) and their nuclei are large and hyperchromatic as seen in (D), confirming this is acral melanoma in situ. (Note: FISH analysis of this lesion revealed amplification of cyclin D1.)
Figure 5. Regular fibrillar pattern composed of thick fibrils. A small brown macule, 4 mm in diameter, seen on the sole of a 38-year-old woman. This fibrillar pattern is composed of regularly arranged thick fibrils, of which endpoints line up on the sulci of the skin markings. Although the color density of the fibrils is somewhat different within the lesion, the color distribution is mostly symmetric, indicating this is the regular FP. From these findings, we can certainly diagnose this lesion as acral nevus. Note: These thick fibrils indicate that melanocytes in the epidermis are not distributed as solitary units but arranged mostly in larger nests, which is an important histopathologic clue to benign nevus of a small size such as this one (4mm).

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Sonographic Characteristics of Leiomyomatous Tumors of Skin and Nail: a Case Series

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Key words: leiomyoma cutis, nail leiomyosarcoma, cutaneous leiomyoma ultrasound, leiomyosarcoma nail ultrasound, dermatologic ultrasound

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ABSTRACT

Introduction: The clinical appearance of the uncommon cutaneous leiomyomatous tumors (LMT) is nonspecific, leading to an extensive differential diagnosis. A non-invasive tool such as high-frequency ultrasound (HFUS) is required for characterizing LMTs in the clinical setting. Although the sonographic features of their uterine counterpart had been well reported, there are only scant reports on the use of ultrasound for studying leiomyomatous neoplasms of the skin and nail.

Objectives: To identify and well characterize common sonographic features of LMT.

Methods: A retrospective analysis of HFUS images of LMT in three different patients, two of them with multiple cutaneous leiomyomas and another with a subungual leiomyosarcoma.

Results: In all cases, several shared ultrasound characteristics were found. Moreover, we describe a new ultrasonographic sign in cutaneous leiomyomas called the “pine tree” sign, with other features not previously reported.

Conclusions: These ultrasonographic characteristics would strengthen the clinical diagnosis, assist with treatment management, and may help avoid serial biopsies in cases with multiple cutaneous lesions.
Introduction

Leiomyoma cutis was first described by Rudolf Virchow in 1854, yet their prevalence is still unknown [1]. These uncommon tumors are rarely detected outside the uterus or the gastrointestinal tract [1-4]. Furthermore, cutaneous leiomyosarcomas, the malignant form of these tumors, are even rarer, comprising only 4.0%-6.5% of all soft tissue sarcomas [5-10]. Superficial cutaneous leiomyomas are divided into 3 distinct variants based on the origin of the smooth muscle within the tumor: Angioleiomyoma, the most common form, originates from the tunica media of blood vessels; piloleiomyoma, which arises from the erector pili muscle of the pilosebaceous-unit; and genital leiomyoma, which derives from the network of smooth muscles in the external genitalia [2]. Leiomyosarcoma may also arise from a dermal component such as the erector pili muscle, or a vascular smooth muscle in the hypodermal tissue [3,5-7]. The origin of subungual leiomyomatous tumors is probably from the vascular smooth muscle at the subcutaneous layer since the erector pili muscle is missing in the nail bed [11,12]. To date, reports of digital cutaneous leiomyomas are scarce, and to the best of our knowledge, a presentation of leiomyosarcoma in the nail bed has not been previously reported [11-13].

The clinical appearance of cutaneous leiomyomatous tumors is nonspecific, and therefore, the differential diagnosis is broad, including other benign and malignant lesions, especially soft tissue tumors. Thus, a non-invasive tool to differentiate between these tumors is necessary. In recent years, high-frequency color Doppler ultrasound (HFUS) has been included in the dermatologic clinical practice tools arsenal [14]. This imaging technique provides relevant information about the nature of a lesion, its anatomical location and structures in its vicinity, and the degree of its vascularity. Although a definitive diagnosis of these smooth muscle tumors is made histologically with specific immune-histochemical stains, sonographic evaluation may be of great value for dermatologists and their patients, since the diagnosis may be determined on the spot, without risks or complications, and may potentially replace the need for a skin biopsy [4,7,8].

We herein report the common and unique ultrasonographic features of 3 patients with cutaneous smooth muscle tumors: 2 with sporadic multiple cutaneous leiomyomas and the third with a rare subungual leiomyosarcoma.

Objectives

The aim of our study was to identify and characterize shared sonographic features of the rare cutaneous leiomyomatous tumors.

Methods

All patients were evaluated by dermatologists and underwent a high-frequency color Doppler ultrasound examination with a LOGIQ E9 XD Clear device (General Electric Health Systems) using linear and compact linear probes working with an upper frequency of 15 MHz and 18MHz, respectively. A copious amount of gel was used to contact the skin with the probe, and the protocol of the examination followed the published guidelines for performing dermatologic ultrasound examinations [15]. Our Institutional Review Board excludes the review of case series with five or fewer cases; however, according to the institutional protocol, the patients provided signed informed consent for the publication of their clinical and ultrasonographic data as well as their histological images. Moreover, ultrasound examinations followed the Helsinki principles of medical ethics.

Results

Case 1

A healthy 32-year-old male presented to our clinic with a 16-year history of tender and firm multiple erythematous nodules on the anterior-medial aspect of his left leg without a history of trauma or infection (Figure 1A). On sonography, several focal, deeply hypoechoic, solid, pseudo-nodular structures of different sizes located in the dermis and predominantly the hypodermis were detected. Some of these nodules showed an ill-defined area at the periphery with hypoechoic pseudo-tubular structures and a posterior acoustic reinforcement artifact. Some of these pseudo-tubules resembled branches of a pine tree and therefore named the “pine tree” sign. Few punctate hyperechoic spots were seen, but neither signs of gross calcifications with posterior acoustic shadowing artifact nor perilesional edema were detected. On color Doppler, low flow arterial and venous vessels were detected at the periphery and within these hypoechoic structures (Figure 1, B-D). The histology was compatible with cutaneous leiomyoma.

Case 2

A 36-year-old male presented at our clinic with a 9-year history of multiple, persistent, and slightly tender pink nodules on his trunk, right arm, and both legs (Figure 2A). The patient denied any systemic symptoms or relevant family history. Sonographic features uncovered multiple oval, round, and slightly lobulated deeply hypoechoic structures with somewhat heterogeneous areas of variable sizes, located in the dermis and hypodermis. These structures generated a posterior acoustic reinforcement artifact and presented some punctate hyperechoic spots (Figure 2, B-D). Neither signs of gross calcifications nor perilesional edema were detected. On
A 32-year-old man with multiple cutaneous leiomyomas in case 1. (B and C grayscale; D, color Doppler). (A) Clinical photograph. (B) Dermal and hypodermal network (*) of hypoechoic bundles (arrows). (C) Dermal and hypodermal pseudo-nodular hypoechoic structure with peripheral bundles (arrows) that resembles a “pine tree”. (D) Dermal and hypodermal hypoechoic nodular structure with tiny peripheral bundles (arrows). Notice the moderate internal and peripheral vascularity.

color Doppler, lesional and perilesional low flow arterial and venous vessels were observed. Both clinically and ultrasonographically was compatible with cutaneous leiomyomatosis.

Case 3
A 31-year-old healthy female presented to the clinic with a two-year history of tender swelling at the nail region of her right first toe. Her physical examination revealed a firm, pink-colored, tender subungual nodule. On ultrasound, a hypodermal deeply hypoechoic solid structure involving the nail bed and the hyponychium was observed, adjacent to the bony margin of the distal phalanx (Figure 3A). Some punctate hyperechoic spots were detected inside the lesion. Increased thickness and decreased echogenicity of
Figure 2. 36-year-old man with multiple leiomyomas in case 2. (B-D, color Doppler). (A) Clinical image. (B) Dermal pseudo-nodular structure (*) with peripheral bundles (arrowheads) that may resemble a distorted “pine tree”. (C) Dermal nodule (*) with small and isolates peripheral bundle (arrowhead). (D) dermal and hypodermal lobulated and hypoechoic structure (*) with peripheral bundles (arrowheads). In B-D there are internal Band peripheral vessels.

the nail bed were seen. The nail plate was displaced upward and maintained its bilaminar structure. Some irregularities and a lack of the distal part of the bony margin of the distal phalanx were demonstrated. On color Doppler, the lesion showed low flow arterial vessels (Figure 3, B-D). The histologic diagnosis was compatible with a subungual leiomyosarcoma with a high mitotic rate and increased cellularity. The patient went through 2 surgeries due to the recurrence of the tumor and later an amputation of the toe. A thorough imaging evaluation didn’t reveal any systemic metastases.

The ultrasonographic features of the cutaneous smooth muscle tumors (Table 1) include multiple dermal and predominantly hypodermal deeply hypoechoic solid structures with posterior acoustic reinforcement artifact and internal low flow vascularity. The hypodermal central part tends to be well-defined and contains hyperechoic spots within it. No evidence of edema or gross calcifications were noted in any of the 3 cases. In the periphery of the nodules, there are hypoechoic pseudo-tubules that can protrude into the dermis, creating a “pine tree” sign on sonography.

Conclusions

Our results clearly demonstrate common and particular sonographic features of leiomyomatous tumors. Clinically, these tumors appear as a firm, pink to brown color papule or nodule, located mostly on the extremities or trunk, and may be painful in up to 75% of patients [1,3,4]. In some patients, multiple cutaneous leiomyomas may be the initial presentation. These leiomyoma multiplex may occur sporadically or may be part of Reed syndrome [5,6,16]. The latter is inherited in an autosomal dominant manner due to a mutation in the gene that encodes fumarate hydratase, an enzyme of the Krebs cycle, and is composed of cutaneous and uterine leiomyomas and renal cell carcinoma [6,15].

Regarding our ungual case, longitudinal band, yellow discoloration, and distal onycholysis are possible, nonspecific, clinical manifestations of this unique subungual mass[11-13]. Accordingly, the nonspecific clinical characteristics of cutaneous tumors may be potent simulators of other dermatologic entities such as cutaneous sweat glands tumors, sarcoidosis, and neurofibromatosis, among other
Figure 3. 32-year-old woman with periungual and subungual leiomyosarcoma in case 3. (A) Clinical photograph shows swelling and erythema of the hyponychium. (B-D). Ultrasound images (longitudinal views; B and C, color Doppler ultrasound, B at 18 MHz; C, zoom of the distal part at 22 MHz and D, greyscale with color filter) show hypoechoic structure at the hyponychium that involves the nail bed. (C) Notice the hypoechoic peripheral bundles (arrows) that protrude into the dermis of the hyponychium. (B and D). 5 small fracture (oblique large arrow pointing up) and a missing distal part of the distal phalanx. Additionally, in B and D, there are hypoechoic peripheral bundles (short arrows and arrowheads). (B and c) Low grade of vascularity. DP = distal phalanx; IP = interphalangeal joint; PP = proximal phalanx; NB = nail bed.

Table 1. Sonographic Characteristics of Leiomyomatous Tumors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
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<tr>
<td>Dermal and hypodermal hypoechoic well-defined solid structure</td>
<td>Psuedo-tubules at the lesion’s periphery. May protrude to dermis, creating the “pine tree” sign</td>
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<tr>
<td>Hyperechoic spots within the lesion without acoustic shadow</td>
<td>Posterior acoustic reinforcement artifact</td>
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<tr>
<td>Internal mild-moderate low flow vascularity on color Doppler</td>
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conditions [1-3,9,10]. Therefore, the use of HFUS may assist in differentiating between these conditions (Table 2). For instance, in contrast to leiomyoma, an intact epidermal cyst also demonstrates posterior acoustic enhancement without internal vascularity. In case of a ruptured cyst, internal vascularity is present, but the cyst borders become ill-defined, and there are signs of edema in the surrounding tissue [17].

Cutaneous sarcoidosis, another possible mimicker of leiomyoma cutis, may also present clinically as solitary or multiple papules and nodules. Via ultrasound, hypoechoic dermal and hypodermal nodules can also be detected; however, in sarcoïd nodules, usually, there are signs of edema in the nodules periphery which seems to be absent in smooth muscle tumors [18].

Neurogenic tumors, such as neurofibromas and schwannomas may also present as multiple and painful cutaneous nodules. Their sonographic appearance portrays a dermal or hypodermal ill-defined hypoechoic or heterogeneous mass but may also have a round, oval, or fusiform shape [19]. Hypoechoic neural tracts may be found at their periphery,
The proximal part of the nail bed is a relatively common location. So far, no signs of hypoechoic pseudo-tubules at their periphery or the presence of hyperechoic spots have been reported [10,22].

In comparison to the repeatedly reported sonographic features of uterine leiomyomas, cutaneous leiomyomas features are less well established [23,24]. The ultrasonographic features of cutaneous leiomyomatous tumors present some similarities to their uterine counterparts, such as their predominant hypo-echogenicity and hyperemic spots, mostly hypovascular on color Doppler. However, cutaneous leiomyomas are usually centrally or eccentrically, respectively. Moreover, in schwannomas, hyperechoic spots resulting from real calcifications may be observed, and posterior enhancement may also be detected [2], but none of these neurogenic tumors demonstrate the “pine tree” sign seen in leiomyomas [20].

Other differential diagnoses may include sweat gland tumors such as nodular hidradenomas, which tend to show a mixed echogenicity with anechoic and hypoechoic areas due to their solid-cystic structure. It also frequently presents fluid-fluid levels, known as the “snow falling sign,” and internal vascularity in its hypoechoic part [21].

For the ungual case, the differential ultrasonographic diagnosis includes ungual fibromas that may present as hypoechoic eccentric periungual hypoechoic masses that involve the nail bed. However, posterior acoustic reinforcement artifact, hyperechoic spots or well-defined borders are not commonly part of fibromas sonographic features [10,22].

Glomus tumors, usually located in the ungual region, tend to be well-defined round or oval-shaped hypoechoic subungual nodules with internal hypervascularity. Scalloping of the adjacent bony margin of the distal phalanx is a common trait. The proximal part of the nail bed is a relatively common location. So far, no signs of hypoechoic pseudo-tubules at their periphery or the presence of hyperechoic spots have been reported [10,22].

In comparison to the repeatedly reported sonographic features of uterine leiomyomas, cutaneous leiomyomas features are less well established [23,24]. The ultrasonographic features of cutaneous leiomyomatous tumors present some similarities to their uterine counterparts, such as their predominant hypo-echogenicity and mainly well-defined borders [24]. However, the intensity of the hypo-echogenicity seems to be higher in the cutaneous tumors. Moreover, although the cutaneous lesions were present for many years, there were no sonographic signs of gross calcifications, commonly found in uterine leiomyomas.

Interestingly, our cases present a different sonographic appearance than other cutaneous leiomyoma cases reported in the literature [25-27]. Stock et al described a lesion with a more heterogeneous echogenicity, hypoechoic capsule at the periphery, internal septations, and multiple hyperechoic calcifications [25]. However, cutaneous leiomyomas are usually

<table>
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<tr>
<th>Diagnosis</th>
<th>Sonographic characteristics</th>
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<tr>
<td>Epidermal cyst [9,17]</td>
<td>Round shape anechoic or hypoechoic structure located in the dermis or hypodermis with anechoic epidermal tract, and posterior enhancement. May also have “pseudo-testes” appearance. In case of rupture or inflammation, increased echogenicity of the periphery and increased vascularity is detected with color Doppler.</td>
</tr>
<tr>
<td>Pilomatrixoma [9]</td>
<td>Round or lobulated nodule with a hypoechoic rim and hyperechoic center in the dermis and hypodermis. Hyperechoic spots may be preset within the center of the lesion, creating a “target lesion” appearance. May have acoustic shadow artifact. Vascularity may vary from hypovascular to hypervascular.</td>
</tr>
<tr>
<td>Neurofibroma [19]</td>
<td>Round, oval or fusiform shaped hypoechoic nodules. May be less well defined. Hypoechoic neural tracts can be found centrally. Vascularity may vary from hypovascular to hypervascular.</td>
</tr>
<tr>
<td>Schwannoma [19,20]</td>
<td>Well-defined round or oval shaped hypoechoic or heterogeneous nodule in the subcutaneous tissue with posterior enhancement. Hypoechoic neural tracts can be found eccentrically. Occasionally presenting anechoic areas and hyperechoic spots, mostly hypovascular on color Doppler.</td>
</tr>
<tr>
<td>Dermatofibroma [9,34]</td>
<td>Ill-defined hypoechoic dermal lesions, usually heterogeneous. Frequently hypovascular on color Doppler.</td>
</tr>
<tr>
<td>Lipomatous tumors [9]</td>
<td>Well defined hyperechoic oval or round-shaped structures following the skin layers. Fibrous septa are detected within the lesions, and are usually hypovascular.</td>
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<tr>
<td>Hidradenoma [21]</td>
<td>Well defined, solid cystic dermal and hypodermal structures that tends to show smoothly lobulated borders, an inner solid component, lacunar fluid-filled spaces, septations and moving echoes creating the “snow falling sign”. Slow flow hyper-vasularity is commonly detected within and in the periphery of the lesion.</td>
</tr>
<tr>
<td>Sarcoidosis [18]</td>
<td>Well-demarcated areas with inhomogeneous hypo-echogenicity, surrounded by an edematous zone pressing down on the adjacent subcutaneous tissue (“a mass effect”). Increased vascularity within the lesions and in the surrounding dermis is frequently detected.</td>
</tr>
<tr>
<td>Subungual fibroma [10,14]</td>
<td>Eccentric oval-, round-, fusiform- or polypoid shaped hypoechoic structure, mostly hypovascular on color Doppler.</td>
</tr>
<tr>
<td>Subungual glomus tumor [10,14]</td>
<td>Hypoechoic well defined nodule, centrally located within the nail bed with increased internal vascularity. Scalloping of the bony margin beneath the tumor is a frequent finding.</td>
</tr>
</tbody>
</table>
not encapsulated and rarely present calcifications on histology unless they involve deeper soft tissues or vascular structures [4]. Sardanelli et al also depicted cutaneous leiomyoma as a well-defined subcutaneous homogeneous nodule but with high flow internal vascularity [26]. In the latter case, the leiomyoma originated from a large muscular branch which may explain the hyper-vascular pattern.

Some case reports of cutaneous leiomyosarcoma used ultrasound for their initial evaluation, and similar to our ungual case described it as a well-circumscribed hyperechoic mass that may sometimes show ill-defined borders [28,29]. An important additional finding in our case is the missing part of the distal phalanx margin, a sign that should raise the suspicion of malignancy and must be differentiated from the scalloping that is commonly seen in the bony margin attached to some benign slow-growing ungual tumors [6,13,28].

The presence of the pseudo-tubules, generating the “pine tree “sign, correlates well with the thick bundles of smooth muscle seen on histology [4,33]. Of interest is the presence of a posterior acoustic reinforcement artifact, frequently seen in fluid-filled structures such as epidermal cyst [9]. We postulate that this artifact could be due to the presence of numerous slow-flow vessels within the lesions or increased transmission of the sound waves through the cells of the tumor [10]. Likewise, the origin of the hyperechoic spots within the lesions is not entirely clear. The hyperechoic spots in the leiomyomas and leiomyosarcoma may be due to molecular components because no signs of calcium deposits were detected on histology. As aforementioned above, only a few reports describe this histologic feature in cutaneous leiomyomas, making it less probable to be the cause [29].

Furthermore, this sonographic finding is repeatedly detected in other malignant skin tumors such as basal cell carcinoma (BCC), where they are usually more prominent [30]. Even in BCC, these hyperechoic spots are not thought to represent calcium deposits since calcification is also not a common histological finding in BCC [31]. Alternatively, they are thought to be produced by an increased transmission through the tumoral cells [31]. Worth mentioning that a high number of these hyperechoic spots within BCCs have been reported to be associated with the more aggressive subtypes that present a high-risk of recurrence rates [32].

In conclusion, leiomyoma cutis and nail leiomyosarcoma show ultrasonographic signs that differ from other cutaneous and nail tumors. The provision of these ultrasonographic characteristics can be relevant to improve the precision of their diagnosis and management.

References


Can Immunofluorescence on Skin/Mucosal Scraping Smear for Pemphigus Diagnosis Substitute Direct Immunofluorescence on Skin Biopsy?

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Key words: pemphigus, direct immunofluorescence, sensitivity, specificity, smear

Introduction: Few studies have been conducted on the use of Direct Immunofluorescence (DIF) on skin/mucosal scraping smear for diagnosis of pemphigus disease; however, the diagnostic value of DIF on the smear has not been fully evaluated.

Objectives: The present study was carried out to assess the sensitivity and specificity of DIF on skin/mucosal smear for diagnose of pemphigus in the patients presenting with mucocutaneous erosive lesions.

Methodology: A total of 89 patients including 40 males and 49 females aged between 23 and 80 years old with various bullous disorders were enrolled in the study. For definite diagnosis, all the patients were subjected to lesional biopsy for pathological studies and perilesional biopsy for DIF studies. In all the cases, skin/mucosal scraping smears were prepared from the perilesional healthy skin/mucosa and were stained with immunofluorescence conjugated anti-IgG.

Results: Of 89 patients, 56 (63%) patients were diagnosed with pemphigus. Immunodeposits favoring the pemphigus were demonstrated in the 46 smears of 56 cases of pemphigus (sensitivity of 82%). No case with other types of bullous disease had positive DIF on the smear (specificity of 100%).

Conclusion: The findings of the study showed that the sensitivity of DIF on the smear is not high enough to allow us replacing the conventional DIF with smear-DIF for diagnosis of pemphigus, while the specificity of 100% would allow the unequivocal identification of a subset of patients with pemphigus.
Introduction

Pemphigus as a rare autoimmune blistering disease is characterized by the widespread flaccid blisters and erosions on the skin and mucous membranes [1]. The hallmark of pemphigus is finding the immunoglobulin G (IgG) autoantibodies against the cell surface of keratinocytes. Pemphigus is classified into subtypes based on the main autoantigen involved in the pathogenesis of disease [1]. Detection of IgG autoantibodies raised against the cell surface of keratinocytes is considered as the gold standard for diagnosis of pemphigus. Pemphigus can be differentiated from other vesiculobullous or pustular diseases through detection of these autoantibodies [2]. Direct Immunofluorescence (DIF) examination is the most reliable and sensitive diagnostic test used for all forms of pemphigus. DIF is able to show the IgG and C3 deposition around the epithelial cells, confirming the diagnosis of pemphigus [3].

Durdu et al have demonstrated that the keratinocyte cells obtained by Tzanck smear can be used as a substrate for DIF studies [4]. Obtaining the Tzanck smears is less invasive than skin or mucosal biopsy and would be useful in the pemphigus patients with conjunctiva involvement or inaccessible oral lesions that cannot be biopsied easily [5]. In this technique, preparation of the samples is much more rapid than the conventional DIF and there is no need for specialized equipment such as the cryostat.

Objectives

The current study was performed to investigate the usefulness of DIF on skin scraping smears obtained from intact perilesional skin in the patients with bullous/erosive disorders in order to evaluate the use of skin/mucosal smears as an alternative to skin/mucosal biopsies for diagnosis of pemphigus.

Methods

Patients

The study protocol was approved by the Institutional Ethics Committee and an informed written consent was obtained from all the patients.

A total of 89 consecutive patients with erosive, vesicular, bullous or pustular skin, or mucosal lesions were included in this study. Demographic, clinical and laboratory data including patients age, gender, and lesion location were recorded using a questionnaire. For definite diagnosis, all the patients were subjected to lesional biopsy for pathological studies and perilesional biopsy for DIF studies. In all the cases, smears were prepared from the perilesional healthy skin/mucosa and were stained with immunofluorescence conjugated anti-IgG.

Preparation of the Smears and Application of DIF on the Samples

For preparing the smears, the perilesional skin or mucosa adjacent to the fresh blister or erosion was first anesthetized through the intradermal lidocaine injection and then, they were gently scraped using the small curette. Then, the obtained cellular materials were spread as a thin layer onto at least two glass slides and were air-dried. The prepared smears were sent to the Department of Pathology for staining. Smears were incubated with fluorescein isothiocyanate (FITC)-conjugated goat anti-human IgG (CEDARLANE, lot number: 7201111401) for 30 minutes in a moist chamber at 37 degree temperature. The sections were then washed in Phosphate-buffered saline (PBS) (2 washes of 15 min each), mounted in buffered glycerol, and examined under fluorescent microscope.

Detection of the ring-shaped deposition of IgG on the individual acantholytic cells or the net-like intercellular fluorescence pattern when sheet of cells were present was considered positive for diagnosis of pemphigus (Figure 1).

The immunofluorescence (IF)-stained samples were studied independently by 2 of the authors. They were unaware of the results of the conventional DIF.

Calculation of the Diagnostic Value of IF -Stained Skin/Mucosal Scraping Smears

The parameters including sensitivity (ie the percentage of patients with positive conventional DIF whose IF-stained smear was positive), specificity (ie the percentage of patients with negative conventional DIF whose IF-stained smear was negative), Positive Predictive Value (PPV) (ie the percentage of patients with positive IF-stained smear whose conventional DIF was also positive) and Negative Predictive Value (NPV) (ie, the percentage of patients with negative IF-stained smear whose conventional DIF was also negative) were calculated to determine the diagnostic value of the IF-stained smear (Table 1). Kappa coefficient was calculated to evaluate the concordance of the IF-stained smear and conventional DIF, and the P value of less than 0.05 was considered as statistically significant.

Results

Totally, 89 patients (40 males and 49 females) aged between 23- 80 years were included in this study. Table1 shows the characteristics of the patients and their diagnosis based on the histopathological and conventional DIF results. Classical suprabasal acantholysis at the lesional biopsy and immune

<table>
<thead>
<tr>
<th>Table 1: Characteristics of the Patients and Their Diagnosis Based on Histopathological and Conventional DIF Results</th>
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<td><strong>Patient No.</strong></td>
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Methodology: The study was conducted in a dermatology clinic in a tertiary hospital. A total of 89 consecutive patients with a clinical diagnosis of pemphigus were included in the study. All patients underwent lesional biopsy for histopathological examination and perilesional biopsy for DIF. Smears were prepared using a scraping technique and stained with FITC-conjugated anti-IgG. The diagnostic value of IF-stained smears was evaluated using sensitivity, specificity, PPV, and NPV. A Kappa coefficient was calculated to assess the concordance with conventional DIF. The results show a high diagnostic accuracy of IF-stained smears for pemphigus diagnosis.
Figure 1. Positive direct immunofluorescence examination of skin scraping smear in a patient with pemphigus vulgaris shows immunoglobulin G deposition around the individual acantholytic cells (A) and those in groups (B) (400×).

Table 1. Characteristics of Patients with Bullous/Erosive Lesion

<table>
<thead>
<tr>
<th>Age, years Mean ± SD, range</th>
<th>46.60±12.16, (23-80)</th>
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<tr>
<th>Gender, N(%)</th>
<th>Female 49 (55%)</th>
<th>Male 40 (45%)</th>
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<tr>
<th>Diagnosis</th>
<th>Pemphigus 56</th>
<th>Vulgaris 54</th>
<th>Follicaceous 2</th>
<th>Bullous pemphigoid 6</th>
<th>TEN 3</th>
<th>Erythema multiforme 3</th>
<th>Fixed drug eruption 7</th>
<th>Herpes zoster 3</th>
<th>Chicken pox 3</th>
<th>Bullous impetigo 2</th>
<th>Bite reaction 1</th>
<th>Acute eczema 3</th>
<th>Sweet syndrome 1</th>
<th>Pustular psoriasis 1</th>
</tr>
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<tbody>
<tr>
<td>Diagnosis of patient with bullous disease based on histopathology of lesional samples, N</td>
<td>56 (100%)</td>
<td>54</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>3</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Intraepidermal Positive DIF on perilesional punch biopsy sample N(%)</td>
<td>46 (82%)</td>
<td>44</td>
<td>2</td>
<td>0(0%)</td>
<td>0(0%)</td>
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<tr>
<td>Positive DIF on perilesional scraping smear N(%)</td>
<td>46 (82%)</td>
<td>44</td>
<td>2</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
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</table>

Site of obtaining smear or biopsy for IF study N(%)

<table>
<thead>
<tr>
<th>Site of obtaining smear or biopsy for IF study</th>
<th>Oral mucosa 19 (21%)</th>
<th>Extremities 9 (10%)</th>
<th>trunk 40 (45%)</th>
<th>Scalp 21 (24%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>16</td>
<td>2</td>
<td>18</td>
<td>20</td>
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<tr>
<td></td>
<td>12</td>
<td>2</td>
<td>14</td>
<td>18</td>
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DIF = Direct Immunofluorescence; IF = Immunofluorescence; SD = standard deviation; TEN = Toxic Epidermal; Necrolysis.

Deposition compatible with the diagnosis of pemphigus (intercellular lattice-like pattern) were demonstrated in the IgG–stained perilesional biopsies of 56 cases.

IF on the smear was positive in 46 (82%) patients with pemphigus. IF on the smear had a sensitivity of 0.82 (95% Confidence Interval [CI] 0.72-0.92), a specificity of 1.00.
Table 2. Distribution of Frequency of Dif on Tzank Smear and Conventional Dif on Skin/Mucosa Biopsy in Patients with Bullous/Erosive Lesions.

<table>
<thead>
<tr>
<th>Results of DIF on Tzank smear</th>
<th>Result of conventional DIF (golden criteria for pemphigus diagnosis)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Positive, N(%)</td>
</tr>
<tr>
<td>Positive, N(%)</td>
<td>46 (82%)</td>
</tr>
<tr>
<td>Negative, N(%)</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>Total N(%)</td>
<td>56 (100%)</td>
</tr>
</tbody>
</table>

Kappa = 0.773 P < 0.001
DIF = Direct Immunofluorescence.

(95% CI 1.00-1.00), a PPV of 1.00 (95% CI 1.00-1.00), and a NPV of 0.77 (95% CI 0.64-0.89). A significant concordance was found between the results of IF-stained smears and those prepared by the conventional DIF for diagnosis of pemphigus (Kappa = 0.773, P < 0.001). Table 2 presents the data on IF-stained smears and those prepared by the conventional DIF.

Conclusions

Lesional skin/mucosal scraping called Tzanck smear is generally used for diagnosis of the Herpes Simplex Virus infections [6]. The presence of acantholytic cells accompanied by multinucleated giant cells is a characteristic cytological finding for diagnosis of herpetic infections [6]. This method has also been suggested as a simple and rapid technique to be used in diagnosis of pemphigus disease [6]. Cytological examination of the smears obtained from scraping of floor of the blisters in the pemphigus patients has shown the presence of typical acantholytic cells (or Tzanck cells). These cells are not pathognomonic for the pemphigus and are commonly observed in other types of bullous disease such as Hailey-Hailey disease and herpetic infections [6]. The cyto-diagnosis is not extensively used due to low specificity of this technique in diagnosis of the pemphigus. Positivity of acantholytic cells in the cases with pemphigus has been reported by 96.7%-100% while, the specificity of acantholytic cells for pemphigus has been reported by 43.3%-60% [4,6]. This means that, if we rely on the use of Tzanck smear alone, 40%-60% of the cases presented with erosive and bullous eruptions would falsely be diagnosed as pemphigus. Then, for definite diagnosis of pemphigus, autoantibodies raised against the epithelial cell membrane have to be detected by applying the DIF staining [3].

DIF analysis of the perilesional skin biopsy is the most accurate approach for diagnosis of pemphigus, showing IgG deposits on the surface of keratinocytes [3]. The direct immunofluorescence test on Tzanck smears has been proposed as a simple alternative to skin biopsy for diagnosis of pemphigus [4]. DIF examination of a Tzanck smear shows bright green fluorescence at the cell margins of single acantholytic cell or in the intercellular region in the case of cell clumps, compatible with positive IF pattern of pemphigus [4]. Although, the IF examination of skin scraping smear seems a simple and practical cytological technique for diagnosis of pemphigus, there is a limited evidence on the relative sensitivity and specificity of DIF on the smear compared to the DIF on skin biopsy as a gold standard.

According to the review of the literature, there are a few related studies with divergent results in this context. Durdu et al have reported about the typical IgG deposit around the acantholytic keratinocytes in the Tzanck smears of all (100%) the 20 patients with pemphigus [4]. Nonetheless, Aithal et al have shown that among 12 pemphigus patients with positive DIF on the skin biopsy, only 6 of them (50%) had positive DIF on the Tzanck smear [8].

In the current study, the result of DIF examination on the smear was positive in 46 (82%) of the pemphigus patients (out of 56 patients). Ten patients had negative results. The larger sample size or technical issue in the IF staining of the smears might explain observing these 10 false negative results.

It also could be attributed to the fact that the smears were taken from the healthy perilesional skin and not from the blister floor. In scraping of the intact skin, collected keratinocytes are mostly from the superficial epidermal layers where immune depositions are partly or completely absent in the subset of patients with pemphigus vulgaris. In pemphigus vulgaris, due to the difference in the relative amount of desmoglein 3 in the epidermal layers, occasionally the fluorescence may be limited to or more intense in the lower levels of the epidermis [2].

According to the results, the sensitivity and specificity of DIF on skin/mucosal smear for diagnosis of pemphigus were equal to 82% and 100%, respectively. This sensitivity was not high enough to allow us replacing the conventional DIF on skin biopsy with DIF on skin/mucosal smear, for diagnosis of pemphigus. In other words, approximately 20% of pemphigus patients would be missed if we rely on IF staining on the smear alone. Nonetheless, the observed specificity of 100% allows an extremely high level of confidence to diagnose the pemphigus in the case of positive DIF on the smear.
One limitation of this study is that the only DIF was used as a gold standard to differentiate pemphigus cases from other vesiculobullous diseases. Because of resource limitation anti-desmoglein antibodies were not measured. Then we were unable to compare the diagnostic value of DIF on skin/mucosal smears with enzyme-linked immunosorbent assay for detecting anti-desmoglein 1 and 3.

Given that, DIF on the smear is a less invasive and much cheaper procedure compared to the DIF on biopsy, a plausible approach is that when a clinically suspicious pemphigus patient presents with the bullous lesions first, the DIF examination on the skin scraping smear is performed, and if it is positive then, the diagnosis of pemphigus is confirmed while if, it is negative then, a biopsy must be taken for conventional DIF studies.

References


Nonsurgical Reshaping of the Lower Jaw With Hyaluronic Acid Fillers: A Retrospective Case Series

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Key words: filler injection, lower jaw, nonsurgical, multilayer injection, hyaluronic acid


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Nonsurgical aesthetic treatments of the lower face are increasing in demand. In particular, they aim to restore facial youth following the changes due to progressive resorption of facial skeleton and atrophy of facial fat compartments which give the perception of a descent face.

Objectives: The aim of this research is to describe the nonsurgical reshaping of the aged lower jaw by means of hyaluronic acid fillers.

Methods: A retrospective analysis of data from adult female patients undergoing treatment with hyaluronic acid injections in the lower third of the face was performed. Injection techniques, relevant anatomy of the anatomical area and rheological properties of the fillers to be used are highlighted.

Results: Thirty-six consecutive patients were enrolled (100% female; mean age: 45.7 years). A minimum of 4 up to 7 vials of hyaluronic acid filler was injected to achieve the desired results. The visual analogue scale was used to assess patient satisfaction. Thirty-two patients (88.8%) rated their appearance post-treatment with a satisfaction score ranging between 85% and 100%. A total absence of ecchymosis and/or swelling in the early postoperative days has been highlighted. There were no cases of infection, paresthesia, hematoma or necrosis.
Introduction

Facial aging is a complex multifactorial phenomenon that embraces both hard and soft tissues. Over the years, there is a progressive resorption of the facial skeleton characterized by the posterior displacement of the maxilla, and the lateral-inferior shifting of the lateral and inferior orbital rim creating a larger orbital aperture. In the aging process, there is a sort of contraction of the lower jaw in a vertical and a horizontal plane induced by the resorption of the gonial angle, chin symphysis, body and ramus of the jaw. Moreover, we should also consider a possible tooth loss that causes the resorption of the alveolar process contributing thus to an aged appearance [1]. The loss of hard tissue support is accompanied by the overlying soft tissue slipping. Although there are no fat compartments along the lower jaw, but only subcutaneous fat tissue, the deflation of midfacial fat compartments induces soft tissue falling that, associated with the loss of bony projection, contributes to the loss of definition of the jawline [2,3].

Progressive atrophy of facial fat compartments is recorded. Moreover, the attenuation of the zygomatic-cutaneous, orbito-malar, and mandibular retaining ligaments gives the appearance of facial soft tissues descent. As some anatomical studies have confirmed, it acts as a hammock between the atrophied fat compartments and the soft tissues of the face, contributing to the morphological appearance of the tear through deformity, malar bags, and jowling [4].

A deep plane facelift is the surgical gold standard to restore a youthful and natural appearance of the face. Over the last years, an increasing interest in deep plane face lifting techniques has been rising, highlighting the role of facial retaining ligament release and facial fat compartments repositioning [5,6].

However, during the last 20 years, nonsurgical anti-aging facial procedures have gained more and more popularity. Patients have been aiming for natural results with no need for surgical interventions; for this reason, the use of hyaluronic acid (HA) fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; for this reason, the use of hyaluronic acid fillers has shown to be a mainstay among nonsurgical interventions; 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Nowadays, facial fillers are used for a wide range of procedures such as nonsurgical nose job, temple volumization, eyebrow repositioning, etc.

Moreover, HA fillers are even used to restore post-surgical facial deformities, showing a good profile of safety with long term stability [10-13]. The aforementioned issues paved the way for the treatment of certain areas, such as the jawline, that were previously considered nonsuitable for HA filler injections [14].

Objectives

This research aims to describe nonsurgical reshaping of the aged lower jaw by means of hyaluronic acid fillers, highlighting the specifics of fillers and the technique with respect to facial anatomy.

Methods

This retrospective case series includes 36 consecutive patients, seeking nonsurgical lower jaw sculpting, treated by the senior author (RR) from January, 2014 to January, 2020. The study was conformed to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for cohort studies. Every patient signed an informed consent for the procedure and scientific purposes. Only HA-based fillers were used, different brands with different cross-linking agents (1,4-butanediol diglycidyl ether [BDDE] or polyethylene glycol [PEG]) were employed (Nyuma Pharma; Neauvix; Teoxane; Styline, Laboratoires Vivacy). For each brand, different fillers with different rheological properties were chosen according to the anatomical layer to be injected.

Every procedure was performed at least 21 days after the first consultation in an office setting and was not followed by or combined with any other aesthetic treatment. No antibiotic, corticosteroid, painkillers, or other drugs were prescribed to the patients at the end of the procedure. After the injections, an HA-based topical gel was applied on the skin in the treated area, and a HA patch was placed over for 20 minutes to reduce post-injection redness and swelling. Due to the complexity of the injections, it is always recommended to have the patients stay in the waiting room for at least 20-30 minutes after the procedure in order to exclude vascular impairments or any other early adverse event. The patients were evaluated 21 days after the procedure. At this time, the visual analogue scale (VAS) was used to assess patient satisfaction from 100 (the best aesthetic outcome possible) to 0 (the worst). In 3 cases a touch-up

Conclusions: For those patients not willing to undergo surgery, the jawline remodelling with hyaluronic acid fillers seems to be a viable option for ameliorating the definition of the lower third of the face. Nonetheless, it is mandatory to perform multilayer injections using fillers with different rheological properties.
was performed after VAS evaluation, under the physician’s suggestion to address minor asymmetries. Less than 1 mL was required per touch-up.

**Filler Rheology**

To inject over the periosteum, a filler with a G’ over 400 Pa was chosen. While, to inject subcutaneously, a filler with lower G’ between 200 and 300 Pa was chosen. As a general rule, the deeper the injections are (over/under the periosteum) the higher the G’ (storage/elastic modulus) and the G* (hardness) should be. This is the ratio between G’ (storage/elastic modulus) and G” (loss/viscous modulus). On the other hand, the more superficial the injection has to be (dermal layer), the higher the G” and the tan delta (G” and G’ ratio) should be [15].

**Pre-operative Plan and Injection Technique**

After face cleansing with 80% isopropyl alcohol, the symphysis midline was identified on the lower edge of the mandible where the first deep bolus was released with a high G’ filler: about 1.5 cm apart in each side. One more point was marked where the second bolus was released. If 3 points were not enough and jowling was still observed, 1 more point would be marked and injected at about 1.5 cm apart per side, paying careful attention not to go laterally to the mandibular septum. In order to achieve a straight jaw-line, the amount to inject over the periosteum should be higher in the midline compared to the laterally marked points in an ideal pyramid shape (eg if 0.2 mL are injected into the midline, 0.1 mL about 1.5 cm apart on each side has to be injected). Deep perpendicular injections were carried out with a 25 G, 4 cm long needle.

Once deep injections were performed, an over-protruded chin could be identified. In such a case, the labio-mental crease was marked, then 1 triangle per side with the apex pointing towards the labio-mental crease was marked and injected subcutaneously. Using a filler with a lower G’ compared to the deep injections already performed, the injections were carried out with a cannula, filling the labio-mental crease and the 2 triangles previously marked to erase the overprotruded aspect of the chin by pushing forward the soft tissues of the surrounding area. During these injections, the cannula usually encounters some resistance due to the fatty fibrotic tissue represented under the skin of this anatomical area. A 4-cm cannula was used for these 27G injections.

On the gonial angle, a perpendicular injection was performed over the periosteum with the same high G’ filler previously used for the chin. The injection was performed in the most lateral part of the gonial angle to straighten the mandible posteriorly. Then, a lower G’ filler was used to restore the mandible body and ramus. The low G’ filler was the same as the one previously injected into the subcutaneous tissue. To fill the subcutaneous tissue over the body of the jaw, the cannula entry point was performed with a needle, 1 cm ahead of the anterior margin of the masseter, over the lower border of the mandible. Once the cannula is inserted, one or more passages were performed to fill the area with retrograde releasing.

Over the parotid, the ramus area was filled with the same low G’ filler. The entry point was performed ahead of the tragus. The cannula should not be inserted in the superficial subcutaneous layer. The HA was retrogradely released, with one or more passages, over the parotid fascia. In this area, some resistance can be felt in the cannula movements due to the presence of the parotid fascia (Figure 1). Excessively superficial injections in this area usually make the filler visible, leading to unpleasant results. The area between the masseteric cutaneous ligament and the mandibular septum was never injected in order to prevent a worsening of the jowling (Table 1).

**Results**

Thirty-six consecutive patients seeking nonsurgical reshaping of the jaw-line were examined and treated. Every patient was female, age ranging from 42 to 71 years (mean 45.7 years). Minimum follow-up was 3 months, maximum 2 years. A minimum of 4 and up to 7 vials of HA filler was injected to achieve the desired results. Early or tardive adverse events were not reported. A moderate reduction of lower teeth display was recorded in all the patients. However, this issue was clearly explained to the patients before the injections (Figure 2). Patient satisfaction assessment results reported no scores lower than 75. Twelve patients gave a score of 100, 8 patients rated 90, 12 patients indicated a score of 85, 4 patients rated 80, and 2 indicated 75 (Table 2).

Whenever the procedure was carried out with fillers not containing a local anesthetic, patients reported more pain and discomfort than patients who received fillers premixed with a local anesthetic.
**Table 1.** Features of injection sites, hyaluronic acid dose, type of injection, the anatomical layer to be injected, and the needle/cannula use

<table>
<thead>
<tr>
<th>Injection Site</th>
<th>Hyaluronic Acid Injection (Range)</th>
<th>Type of Injection</th>
<th>Anatomical Layer</th>
<th>Needle/Cannula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symphysis</td>
<td>0.2-0.3 mL</td>
<td>Bolus release</td>
<td>Over the periosteum</td>
<td>Needle</td>
</tr>
<tr>
<td>Para-symphysis</td>
<td>0.1-0.2 mL</td>
<td>Bolus release</td>
<td>Over the periosteum</td>
<td>Needle</td>
</tr>
<tr>
<td>Supplementary injections lateral to the para-symphisis (before mandibular septum)</td>
<td>0.1 mL</td>
<td>Bolus release</td>
<td>Over the periosteum</td>
<td>Needle</td>
</tr>
<tr>
<td>Gonial angle</td>
<td>0.3-0.5 mL</td>
<td>Bolus release</td>
<td>Over the periosteum</td>
<td>Needle</td>
</tr>
<tr>
<td>Mandibular ramus</td>
<td>0.5-1 mL</td>
<td>Retrograde release</td>
<td>Subcutaneous tissue (between the SMAS and the parotid fascia)</td>
<td>Cannula</td>
</tr>
<tr>
<td>Mandibular body</td>
<td>0.5-1 mL</td>
<td>Retrograde release</td>
<td>Subcutaneous tissue (under the platysma)</td>
<td>Cannula</td>
</tr>
<tr>
<td>Cutaneous part of the lower lip</td>
<td>1-1.5 mL</td>
<td>Retrograde release</td>
<td>Subcutaneous tissue (fatty fibrotic perioral tissue)</td>
<td>Cannula</td>
</tr>
</tbody>
</table>

SMAS = superficial musculoaponeurotic system.

**Table 2.** Patient satisfaction with hyaluronic acid filler procedure*.

<table>
<thead>
<tr>
<th>VAS Score</th>
<th>100</th>
<th>90</th>
<th>85</th>
<th>80</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>12</td>
<td>8</td>
<td>12</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

*Patients were asked to rate their satisfaction from 0 to 100, with 0 representing the worst possible aesthetic outcome, and 100 representing the best possible aesthetic outcome.

**Conclusions**

A well-defined jawline is an important aesthetic and anatomical landmark to have a clear demarcation between the face and the neck [14]. To achieve natural and pleasant results, it is mandatory for the injector to have a deep knowledge of the facial anatomy and the HA fillers rheology. Using different HA fillers for each facial anatomical layer is required to avoid unnatural results, especially the “detection” of the filler during facial dynamics [9].

Several case series of lower jaw nonsurgical reshaping with the use of fillers are published in medical literature,
even though most of them are not focused on the treatment of the aging mandible [14,16-18]. In a recent paper, Bertossi et al described their experience in the nonsurgical definition of the chin and jawline in younger adults, using a grid system approach.

In 2020, also Mastroluca et al focused on the lower third definition in male patients to achieve a more masculine identity; even in this paper, the focus was not on the reversal of the facial aging process of the lower third [18]. Most published articles about nonsurgical chin and jawline definition are focused on the use of a single filler, usually with a high G’ [17,19]. Nonetheless, it is a demanding treatment that should be approached only by experienced injectors with suitable training. If compared to other face areas there is not so much research focused on it.

The results on our patients show neither early nor tardive adverse events. This is explained by the injection pattern that focuses on relevant anatomical landmarks. Indeed, every deep injection is performed along the anterior edge of the mandible. Consequently, the knowledge of vascular pedicles and nerves of this area is of paramount importance to avoid vascular impairments as well as sensorial and/or motor paresis. As regards the facial artery and mandibular marginal nerve, the use of a cannula is recommended when the body of the mandible has to be injected. The needle “entry point” should be performed superficially above the platysma [20]. Perpendicular injections above the lower edge of the mandible allow to easily avoid ascendant mental artery or mental nerve injuries.

In order to achieve natural results, we approached the lower third using different fillers, with different rheological properties. A similar approach was suggested by Salti, despite he focused on facial mid-third restoration [9]. The use of fillers with different rheological properties in different anatomical facial layers can be considered an anatomical concept that supports the golden rule “like with like” of facial reconstruction [21]. When a filler is implanted deeply over the bone to give projection, it needs to have enough strength to support the overlying tissue (muscles, fat, etc.), avoiding deformation in the facial dynamics. In turn, if soft tissues have to be filled in or pushed forward to avoid the filler visibility in facial animations (smiling, speaking, etc.), it is suggested that the same deeply injected filler not be used but one with a lower G’ so as not to detect it in facial muscle contractions. The role of deep injections with high G’ over the chin could be compared to the role of chin implants: as shown in literature, alloplastic chin implantation can help strengthen and further define a retrusive chin and a weak jawline [22].

Furthermore, an interesting role of this kind of filler is the myomodulation detected at the site of depressor angulis oris and depressor of the lower lip muscles. De Maio firstly identified the role of HA fillers in modifying facial muscles contractions in the peri-oral region to achieve natural and pleasing results and solve aesthetical problems such as gummy smiles or asymmetrical smiling [23]. In the present case series, we identified a reduction of lower teeth displays in all the injected patients; this was easily understood thanks to De Maio findings [24,25]. When HA is injected with a cannula in the triangles marked between the chin and the lower lip, the filler thus reduces the capability of contractions in the depressor angulis oris and in the depressor of the lower lip muscles. This “secondary” effect mimics the mouth corner lift, usually achieved with botulinum toxin injections into the aforementioned muscles [26].

The VAS scale evaluation revealed a high mean of patient satisfaction, also related to the absence of required days off after the procedure and/or swelling in the early postoperative days (Figures 3-8).

Consultation plays a key to achieve high patient satisfaction, especially with naive patients [18]. Usually, patients consider HA fillers as just an “injection” due to information found on the internet or in ads. It is mandatory during the first consultation to let them understand the type of injections performed, potential risks such as vascular impairments, and eventually secondary effects such as lower teeth display reduction that can be detected postoperatively [27].

After advanced filling procedures, it should be mandatory to have the patients waiting in the office for at least 30 minutes following the injections. This has already been described for others areas rich in vascular networks such as the nose [10]. In the present case series, after the injection, an HA-based topical gel was applied over the skin in the treated area, and an HA patch was placed over it for 20 minutes. This care is performed to calm the patient and to have time to detect early complications, such as vascular impairments that may require early hyaluroindase (HYAL) injections [28-30]. However, the application of early HYAL injections always needs to be discussed with patients prior to proceeding with the treatment because if the patient opts out of them, then it would be best not to perform the procedure.

Some papers regarding the use of a single filler or a single brand of fillers to reshape the mandible have been published [14,16-18]. However, in the present paper, we focused on the meaning of knowing the rheological properties of the filler independently from the brand. Almost all facial filler brands have different types of fillers, a correct knowledge of the rheological properties of the filler based on the anatomical layer to be injected allows the physician not to focus only on a certain brand.

Published papers on the same topic mainly address “young adults.” Indeed, Braz et al. concluded that this technique is for patients around 40-45 years old with a beginning of sagging of the lower face (small jowl and visibility the
Figure 3. Lateral view of a 68-year-old patient before (above), and 1 month after injections (below).

Figure 4. Three-quarter view of a 68-year-old patient before (above) and 1 month after the injections (below).
Figure 5. Three-quarter view of a 44-year-old patient before (upper) and 2 years after the injections (below).

Figure 6. Three-quarter view of a 44-year-old patient before (above) and 2 years after the injections (below).
Figure 7. Three-quarter view of a 46-year-old patient before (above) and 3 months after the injections (below).

Figure 8. Three-quarter view of a 46 year old patient before (upper part) and 3 months after the injections (lower part).
mandibular ligament fixed point and a little retrogeneia) or young patients with retrogeneia who do not want to undergo surgery [31]. During this case series, we also evaluated older patients (Figure 3 shows a treated 72-year-old patient) reporting a high score in patient satisfaction. Naturally, not all older patients can benefit from these tridimensional injections. When a patient complains about facial aging, the first suggested option should be a surgical facelift. However, if the patient does not want to undergo surgery but desires to ameliorate the appearance of the jawline, then multilayer HA injections represent a viable option.

The present case series is limited by the evaluation of the results done comparing pre and post-treatment photos and a VAS scale filled out by the patients. Clinical photographs are useful for scientific records and research, despite in standardization and systematization of the photographic positions for the clinical evaluations reliability and reproducibility, the variability is still a matter of fact [32]. Regarding the results of patients’ evaluation, self-perceived aesthetic improvement is one of the most debated issues in aesthetic surgery [33]. The VAS evaluation is widely used in literature and clinical practice. It was used in this work thanks to its simplicity, quickness, smartness, and adaptability. However, seeking measurement bias is crucial, principally when patient satisfaction is taken as an outcome [34].

Multilayer HA injection treatment for lower jaw aging represents a viable option for ameliorating the jaw-line definition in those patients not willing to undergo surgery. Deep knowledge of the relevant anatomy and rheological features of each filler properly used in each anatomical layer is required.

Conflicts of Interest: R.R. is a paid speaker for Neauvia International and works as a consultant for Nyuma Pharma; N.Z. works as scientific coordinator for Neauvia International and consultant for Merz Pharma. P.B. is a paid speaker for Teoxane. Other authors declare no conflict of interest.

References


Introduction: Lichen sclerosus (LS), is an uncommon inflammatory dermatosis with preferential involvement of anogenital region. Diagnosis of LS is mainly clinical, but clinical differentiation from conditions like vitiligo, morphea may be a difficult task at times that often requires histological analysis. Dermoscopy is one such non-invasive tool which can help diagnose the disease. There is paucity of Indian data on dermoscopy of LS.

Objectives: To evaluate clinical, dermatoscopic patterns of LS and correlate them with histopathology.

Methods: The study was conducted in a tertiary hospital after obtaining consent from 20 patients. OITEZ e-scope digital microscope was used to evaluate the lesions. Both polarized and nonpolarized mode were used and skin biopsy was done to confirm diagnosis.

Results: Based on morphology, LS was classified as scleroatrophic lesions (61.5%), guttate lesions (30.8%) and hyperkeratotic lesions (7.7%). Dermoscopic analysis revealed structureless white to yellow areas as most common finding (100%) followed by chrysalis like structure (80.8%). Linear irregular vessels were seen in 61.5% lesions and perifollicular scaling in 50.0% lesions. Keratotic plugs were seen in 50.0% lesions. A new characteristic finding, “rosettes” was seen in 38.5% lesions has never been reported with LS before. Non polarized mode was particularly useful for identifying texture changes, keratotic plugs and minute scales which were not visible otherwise.

Conclusions: Dermoscopy is a simple diagnostic tool that helps in the early diagnosis of LS with specific pattern which can avoid invasive procedure like biopsy. Both non-polarised and polarized dermoscopy must be done to visualize the changes of LS well.

ABSTRACT

Dermoscopic Evaluation of Extragenital Lichen Sclerosus et Atrophicus

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Key words: chrysalis like structure, dermoscopy, extragenital lichen sclerosus et atrophicus, rosettes, white structureless areas

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Introduction

Lichen sclerosus (LS), is an uncommon inflammatory dermatosis with preferential involvement of anogenital region. Isolated extragenital LS is seen in 6% of cases, and association with genital LS seen in 15-20% cases [1]. Women are affected more commonly than men [2]. Extragenital LS - found to be relatively common on the neck and shoulder - is generally asymptomatic, but can occasionally be pruritic [2]. Extragenital LS presents as white polygonal porcelain atrophic papules that coalesce to form plaque studded with comedo-like plugs or evenly spaced dells which corresponds to appendageal ostia [2].

Diagnosis of LS is mainly clinical, and sometimes clinical differentiation from other hypopigmentary conditions such as vitiligo and scleroatrophic disorder like morphea may be a difficult task that often requires histological analysis. Dermoscopy is one such non-invasive tool which can help develop a pattern to diagnose the disease.

Objectives

To study dermoscopic patterns of extragenital LS in series of patients with brown skin and correlate these patterns with histopathology.

Methods

Patients

This was an observational case series study conducted in the Department of Dermatology of a tertiary hospital, from July 2018 to January 2020. A total of 20 patients with clinical features of LS were enrolled in the study. A complete history and dermatological examination were performed after obtaining written informed consent from the patient. Demographic data, such as age, gender, and clinical variables in terms of site of lesions and disease duration were documented. Lesions with less than 2 years and more than 2 years duration were arbitrarily termed as early and late lesions. A first biopsy was taken from clinically active lesion and a second biopsy was taken if patient had genital LS or different morphology of LS.

Dermoscopic examination

OITEZ e-scope digital microscope [DP-M17 filter e-scope pro (optical 200x)] with 20x and 200x magnification was used for dermoscopy and an alcohol-based sanitizer was used as immersion fluid. Both polarized and non-polarized modes were employed in the study. The dermoscopic images were saved and the findings noted on an excel sheet after evaluation by two individual independent authors. Parameters such as vessels, scales, follicular findings, background color, morphology and specific findings if any were noted.

Inclusion criteria

Untreated patients of extragenital LS willing to give consent with histopathology suggestive of the disease were included in the study.

Exclusion criteria

Patients already on treatment for the disease, or not willing for biopsy were excluded from the disease.

Statistical analysis

Statistical analysis was performed using descriptive tools such as percentage and frequency. Results were statistically described as types of dermoscopic patterns.

Results

There were 20 patients (12 females, 8 males) and 26 lesions included in the study. The patients with extragenital LS with mean duration of disease of 20.4 months (minimum 2 months and maximum 6 years) and mean age of 37.8 years (youngest 12 years and oldest 71 years) presented with hypopigmented lesions at different sites. The lesions were asymptomatic in 15 patients and pruritic in 5 patients. On examination the maximum number of lesions were seen on the trunk (101, 38.5%) followed by lower extremities (6, 23.1%), upper extremities (9, 34.2%) and the least on face (1, 3.8%). Koebner phenomenon was seen in 4 patients. Patients presented with classical ivory colored small polygonal papules coalescing to form plaques or hypopigmented atrophic plaques. Four patients also had multiple guttate macules of LS. LS of the genitalia was seen in 3 patients and 2 patients had biopsy-proven morphea in addition. Lesions were classified into 3 groups based on morphology namely scleroatrophic plaque (16) (Figure 1A), guttate (8) (Figure 1B) and hyperkeratotic having predominantly keratotic plugs with underlying sclerosis (2) (Figure 1C). All lesions (Table 1) of extragenital LS revealed patchy structureless white to yellow areas (WSA) (Figure 2A) which were most commonly associated with irregularly arranged linear vessels (16, 61.5%), linear branching vessels (10, 38.5%) or dotted vessels (4, 15.4%) and glomerular vessels (4, 15.4%). The linear vessels were of varying calibers, whereas dotted vessels were arranged in a random fashion. Erythematous areas were seen in 10 (38.5%) lesions which were accompanied by vessels. Chrysalis like structure which is shiny white streaks was seen in 21 (80.8%) patients (Figure 2B). Comedone-like opening (CLO) defined as ovoid or round craters filled with brownish-black material were seen in 9 (34.6%) lesions whereas keratotic plugs defined as invaginations filled by yellowish material were seen in 13 (50.0%) sites (Figure 3, A and B). Peppering blue grey dots was seen in 9 (34.6%) lesions (Figure 3, C and D).
Figure 1. (A) Two shiny porcelain white colored atrophic plaques on axilla typical of scleroatrophic plaque of Lichen sclerosus (LS). (B) Multiple discrete hypopigmented rain drop like slightly atrophic macules typical of guttate lesions of LS. (C) Multiple hypopigmented sclerotic guttate lesions coalescing to form plaques studded with multiple Comedone-like openings typical of hyperkeratotic LS.

Table 1. Morphology and duration wise distribution of dermoscopic findings

<table>
<thead>
<tr>
<th>Dermoscopic findings, N (%)</th>
<th>Total (N)</th>
<th>Scleroatrophic plaques (N = 16)</th>
<th>Guttate (N = 8)</th>
<th>Hyperkeratotic plaques (N = 2)</th>
<th>Duration ≤ 2 years (N = 20)</th>
<th>Duration &gt;2 years (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White structure-less areas</td>
<td>26</td>
<td>16 (100%)</td>
<td>8 (100%)</td>
<td>2 (100%)</td>
<td>20 (100%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Chrysalis structures</td>
<td>21</td>
<td>13 (81.3%)</td>
<td>6 (75.0%)</td>
<td>2 (100%)</td>
<td>16 (80.0%)</td>
<td>5 (83.3%)</td>
</tr>
<tr>
<td>Linear irregular vessels</td>
<td>16</td>
<td>10 (62.5%)</td>
<td>5 (62.5%)</td>
<td>1 (50.0%)</td>
<td>13 (65.0%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>Perifollicular scales</td>
<td>13</td>
<td>8 (50.0%)</td>
<td>4 (50.0%)</td>
<td>1 (50.0%)</td>
<td>9 (45.0%)</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>Keratotic plug</td>
<td>13</td>
<td>6 (37.5%)</td>
<td>5 (62.5%)</td>
<td>2 (100%)</td>
<td>10 (50.0%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>Erythematous areas</td>
<td>10</td>
<td>6 (37.5%)</td>
<td>2 (25.0%)</td>
<td>01 (50.0%)</td>
<td>9 (45.0%)</td>
<td>1 (16.6%)</td>
</tr>
<tr>
<td>Rosettes</td>
<td>10</td>
<td>5 (31.3%)</td>
<td>5 (62.5%)</td>
<td>1 (50.0%)</td>
<td>8 (40.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Comedo-like openings</td>
<td>9</td>
<td>5 (31.3%)</td>
<td>2 (25.0%)</td>
<td>2 (100%)</td>
<td>6 (30.0%)</td>
<td>3 (50.0%)</td>
</tr>
<tr>
<td>Peppering of pigment</td>
<td>9</td>
<td>5 (31.3%)</td>
<td>4 (50.0%)</td>
<td>0</td>
<td>06 (30%)</td>
<td>3 (50.0%)</td>
</tr>
</tbody>
</table>

Peri-follicular scales were observed in 13 (50.0%) lesions, generalized white colored scales in 12 (46.2%) lesions and collarette like in 2 (7.7%) lesions (Figure 4). Pigment network was seen in 1 (3.8%) patient. Fibrotic beams and erosions were absent in our patients. Hemorrhagic spots were seen in a single patient.

We found that non-polarizer mode was particularly useful for identifying texture change (due to sclerosis), CLO and minute
Figure 2. (A) Dermoscopy of scleroatrophic lesion with OITEZ e-scope digital microscope (20x magnification) suggestive of white to yellow structureless areas (yellow arrow) studded with multiple keratotic yellow-white plugs (blue star), chrysalis like structure (green triangle) and linear irregular vessels (red arrow). (B) Chrysalis structures (red arrow) seen on polarizer mode (20x) characterized by bright white orthogonal linear streaks seen only on polarized dermoscopy is suggestive of underlying dermal collagen homogenization.

Figure 3. (A) Comedone-like openings (red arrow) and yellowish-white keratotic follicular plugs (yellow arrow) seen on polarizer mode (20x). (B) Better appreciated on non-polarizer mode. (C,D) Peppering blue-gray dots suggestive of melanin incontinence seen on polarizer mode (100x).

scales which were not visible otherwise (Figure 3, B and D). In addition, we observed stretched eccrine openings and rosettes on polarized mode. Rosettes defined as 4 white points, arranged as a 4 leaf clover were seen in 10 (38.4%) lesions (Figure 5). In few patients with multiple CLO, we noticed that there was central clustering with radial arrangement (Figure 6).
Conclusions

Histopathological examination findings of 21 biopsied lesions are enlisted in Table 2 (Figure 7).

Dermoscopy-aided algorithm of inflammatory disorders are defined by their characteristics based on background color, vessel morphology and distribution, follicular involvement, surface changes such as scales and disease specific additional clues. Dermoscopy hallmarks of LS on polarizing mode include WSA with linear and dotted vessels suggestive of active lesion [3]. Keratotic plugs suggestive of follicular plugging [3]. Chrysalis like structures are seen as shiny, bright white orthogonal linear streaks which are also commonly observed.
Figure 6. (A,B) central clustering with radial arrangement of comedone-like openings (CLO) and keratotic plugs. (C) Stretched eccrine openings suggestive of stretched acrosyringia due to upper dermal sclerosis and atrophic epidermis seen on polarizer mode (200x). (D) Grouping of CLO in coalescing atrophic papules of LS described as corymbiform pattern seen on non-polarizer mode (200x).

Table 2. Histopathology findings (N = 21)

<table>
<thead>
<tr>
<th>Histopathology findings</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkeratosis</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>Collagen homogenization</td>
<td>17 (80.9%)</td>
</tr>
<tr>
<td>Perivascular infiltrate</td>
<td>13 (61.9%)</td>
</tr>
<tr>
<td>Epidermal atrophy</td>
<td>13 (61.9%)</td>
</tr>
<tr>
<td>Dilated lymphatics</td>
<td>12 (57.1%)</td>
</tr>
<tr>
<td>Vacuolar interface</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>Follicular plugs</td>
<td>10 (47.6%)</td>
</tr>
<tr>
<td>Melanophages</td>
<td>9 (42.9%)</td>
</tr>
<tr>
<td>Band like infiltrate</td>
<td>7 (33.3%)</td>
</tr>
<tr>
<td>Papillary dermal edema</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Dilated blood vessels</td>
<td>4 (19.0%)</td>
</tr>
<tr>
<td>Perifollicular infiltrate</td>
<td>3 (14.3%)</td>
</tr>
</tbody>
</table>

Dermoscopic features of LS correlate with histopathological findings such as WSA and correspond to epidermal atrophy and dense diffuse hyalinization of superficial dermis [5]. CLO is suggestive of dells which correspond to appendageal ostia [5,6]. Chrysalis structures are due to increased collagen deposition [4]. Scaling seen in LS lesions corresponds to hyperkeratosis while the peppering blue gray dots correspond to melanin incontinence seen after vacuolar interface dermatitis. Telangiectasia and dotted vessels represent the easy visibility of vessels due to inflammation from an atrophic epidermis [5]. Rosettes are a form of white shiny structures or are white shiny lines and white shiny areas. White shiny areas and lines have been correlated to dermal in dermatofibroma, Spitz nevus, melanoma and basal cell carcinoma [4].
fibrosis whereas exact correlation of rosette is unknown. It has been suggested that interaction of the polarized light with narrowed or keratin-filled adnexal openings could be the morphological correlation toward formation of rosettes. Rosettes have been linked histologically with alternating focal hyperkeratosis and normal corneal layer and keratin-filled openings. Haspeslagh et al, in transverse sections, provide evidence that smaller rosettes are mainly caused by polarizing horny material at infundibular level in adnexal openings and larger rosettes mainly by concentric peril follicular fibrosis. We believe that rosette in case of LS will be due to same reasons [7]. Dermoscopy of LS on non-polarizing mode is a useful adjunct to observe scaling, tiny CLO and keratotic plugs which aid in diagnosis. The closest mimicker of LS clinically and histopathologically is morphea, which can be differentiated by dermoscopy. Shim et al found a statistically significance for WSA and CLO in LS whereas fibrotic beams crossed by spreading telangiectasia for morphea [8].

WSA were seen in all patients of our study similar to Liu et al and Borges et al whereas it was seen in 88.6% patients in a study by Errichetti et al [6,9,10]. Shim et al reported much lesser percentage (66.7%) of WSA [8]. CLO was seen in 34.6% of patients which was lesser than Shim et al (77.8%) [8]. The most common vessel morphology observed in our study was linear irregular vessels (61.53%) which was less compared to Liu et al (72.8%) and higher than Errichetti et al (25.7%) [6,9]. Dotted vessels were observed in 15.4% patients which was similar to Liu et al (16.8%), Borges et al (13.3%), lesser as compared to Errichetti et al (28.6%) and higher as compared to Shim et al (5.6%) [6,8,9,10]. Chrysalis-like structure suggestive of collagen deposition was seen in 80.8% study participants which was comparable to study by Liu et al (84%) and lower in study by Errichetti et al (40%) and Borges et al (26.7%) [6,9,10] (Table 3).

Scaling particularly peri-follicular (50.0%) represented a very common feature of LS in our study which was less as compared to previous study [6]. Early lesions of LS show keratotic plugs on dermoscopy whereas older ones demonstrate chrysalis like structure [10]. However, in our study there was not much difference in these 2 parameters, instead we saw that vascular findings like irregular linear vessels, and erythematous areas were more frequent in early lesions. Peppering blue-gray dots suggestive of melanin incontinence was seen more frequently in old lesions of LS probably indicating lesion inactivity (Table 1).

Rosettes are a particular finding we want to highlight that has not been described before with LS. Stretched eccrine openings represent stretched acrosyringia of the eccrine glands due to sclerosis of the upper dermis and atrophy of the epidermis. The grouping of CLO in coalescing atrophic papules of LS better visualized on dermoscopy has been described as cribriform or corymbiform [2].

On dermoscopy keratotic plugging was seen in more number compared to follicular plugging on histopathology. This could be because the keratin filled craters correspond to adnexal (eccrine and follicular openings) which may not always be visualized in a particular section of skin biopsy. Broader band of hyalinization was associated with prominent chrysalis like structures.

Limitations of our study were the small sample size, the fact we couldn’t study multiple lesions on the same patient and do their biopsies to correlate their results with dermoscopic findings.

![Figure 7. Histopathology examination of Lichen sclerosus (H&E, 20x magnification) shows hyperkeratosis (red arrow), follicular plugging (yellow star), atrophy of epidermis with flattening of rete ridges (green arrow), focal basal cell degeneration (blue triangle), subepidermal band of homogenization (black arrow) corresponding to the sclerosis with a lichenoid infiltrate of lymphocytes beneath it (white arrow) and dilated lymphatics (orange arrow).]
In conclusion, LS is a rare disorder that can be difficult to differentiate clinically from a number of disorders of hypopigmentation and sclero-atrophic disorders, and hence requires skin biopsy. Dermoscopy is a simple diagnostic tool that helps in the early diagnosis of LS with specific and characteristic patterns which can avoid invasive procedure like biopsy. Both non-polarized and polarized dermoscopy must be done to visualize the changes of LS well. Larger sample size study is required to ascertain the newer dermoscopic findings.

### References


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<tr>
<td>White structureless areas</td>
<td>26(100)</td>
<td>31 (88.6)</td>
<td>12(66.7)</td>
<td>124(99.2)</td>
<td>15(100)</td>
</tr>
<tr>
<td>Chrysalis like structure</td>
<td>21(80.8)</td>
<td>14 (40.0)</td>
<td>--</td>
<td>105(84.0)</td>
<td>4(26.7)</td>
</tr>
<tr>
<td>Linear irregular vessels</td>
<td>16(61.5)</td>
<td>9 (25.7)</td>
<td>--</td>
<td>91(72.8)</td>
<td>--</td>
</tr>
<tr>
<td>Yellowish-white keratotic</td>
<td>13(50.0)</td>
<td>28(80.0)</td>
<td>--</td>
<td>63(50.4)</td>
<td>5(33.3)</td>
</tr>
<tr>
<td>follicular plugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scales (perifollicular)</td>
<td>13(50.0)</td>
<td>15 (42.9)</td>
<td>--</td>
<td>--</td>
<td>9 (60.0%) (type</td>
</tr>
<tr>
<td>Linear branching vessels</td>
<td>10(38.5)</td>
<td>1(2.9)</td>
<td>9(50.0)</td>
<td>--</td>
<td>5(33.3)</td>
</tr>
<tr>
<td>Comedone-like openings</td>
<td>9(34.6)</td>
<td>1(2.9)</td>
<td>14(77.8)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Dotted vessels</td>
<td>4(15.4)</td>
<td>10(28.6)</td>
<td>1(5.6)</td>
<td>21(16.8)</td>
<td>2 (13.3)</td>
</tr>
</tbody>
</table>

### Table 3. Dermoscopic profile of Lichen sclerosus and comparison with other published data


ABSTRACT

Introduction: In the new circumstances of coronavirus disease 2019 pandemic, tele-dermatology and tele-dermoscopy have become more important in daily practice for departments for which visuality is at the forefront as dermatology and plastic and reconstructive surgery.

Objectives: This study was aimed to determine diagnostic accuracy and treatment approaches of non-melanocytic skin lesions between 2 clinics by store and forward tele-dermatology method and to evaluate the contribution of tele-dermoscopy to the diagnostic accuracy for dermatologists.

Methods: A total of 26 patients with non-melanocytic skin lesions were included in the study. Clinical images of the lesions were sent by email to 3 plastic surgeons and 3 dermatologists. The accuracy of the diagnoses was evaluated by comparing tele-dermatology with histopathology. Diagnosis and treatment approaches were recorded for both clinics. Dermatologists also defined their diagnosis with tele-dermoscopic images.

Results: The mean percentage of diagnostic accuracy among dermatologists was 74.3% and among plastic surgeons was 61.5%. There was no significant difference in diagnostic accuracy between departments (P = 0.625). There was a statistically significant difference between the departments for diagnostic and treatment approaches (P values respectively P = 0.002, P < 0.001). Plastic surgeons preferred to confirm their pre-diagnosis histopathologically more than dermatologists. Plastic surgeons recommended...
Introduction

Telemedicine (TM), defined as practicing medicine at a distance, has grown in popularity over the past ten years [1]. As social distancing becoming the new standard in the era of Coronavirus disease 2019 (COVID-19) pandemic, TM emerges as a key tool in medicine. It can be performed with live interaction technology via videoconferencing equipment or with store-and-forward methods via transmitting digital images or photographs of the lesions with patient clinical history [2,3].

TM has a particular value in specialties which have a strong visual aspect, such as dermatology and plastic and reconstructive surgery (PRS) [4]. TM applications among plastic surgeons was observed particularly in the management of various conditions such as acute trauma, burns, and postoperative monitoring [5-8]. Tele-dermatology (TD) has been used since 1995 as an example of TM [9]. TD is a useful alternative where specialized dermatological assistance is not available and has been used successfully to support health professionals worldwide, in either an asynchronous store-and-forward format or a real-time video conferencing format [10].

The majority of TD studies were related to skin cancers in the literature [11-14]. Dermoscopy is a non-invasive tool for originally developed for diagnosing and detecting skin cancer. It has been shown that dermoscopy can be used in the diagnosis of pigmented and non-pigmented skin lesions over time. Tele-dermoscopy (TDS) is a currently defined method that aims to increase diagnostic accuracy by adding dermoscopic images to TD [15]. Most of the research with TDS focuses on melanocytic skin lesions including melanoma and melanocytic nevus. There have been only a few reports with TD and TDS to diagnose non-melanocytic skin lesions (NMSLs) [2,11,15].

Face to face (FTF) comparisons of diagnostic accuracy and therapeutic approaches between dermatologists and plastic surgeons have controversial results [16-18]. To the best of our knowledge there is no study in English-language literature comparing the diagnostic accuracy and differences in treatment approach for NMSLs between dermatology and PRS departments by using TD.

Objectives

The aim of this study was to evaluate diagnostic accuracy rates and treatment approaches of dermatologists and plastic surgeons in NMSLs by using TM and the contribution of the TDS method to the diagnostic accuracy of dermatologists.

Methods

Patients who applied to the dermatology unit of a tertiary oncology hospital in Turkey and were performed a diagnostic skin biopsy between April 2018 and March 2019 were included in the study. Patients who were under 18 years old, pregnant and not volunteers were not involved. Informed consent was taken from each patient and the protocol was approved by a local research and ethics review committee.

Lesions of the patients were examined and recorded by the same dermatologist (BT) who took clinical and dermoscopic pictures of the lesions by using her same mobile phone (iPhone 7s, Apple Inc) and dermoscopy device with connection kit (DermLite DL3N, 3Gen Inc). Lesions with clinical and dermoscopic photographs which required histopathologic examination for differential diagnosis were included in the study. Histopathologic examination was accepted as gold standard for diagnostic accuracy in the present study. Age, gender, duration and localization of the lesions, clinical and histopathological diagnoses, clinical and dermoscopic images were recorded. The evaluation was performed using TD with SAF method. Clinical images and a brief clinical history were sent by email to 6 physicians, namely 3 plastic surgeons and 3 dermatologists. Each physician was 8 to 15 years experienced within his/her specialty. All dermatologists had completed a dermoscopy course before the study.

Physicians were asked to record their clinical diagnosis, which was then compared with the histopathological diagnosis. It was also questioned whether they need to confirm the diagnosis with histopathology and which treatment approaches such as excision, cryotherapy, electrotherapy or laser therapy would prefer. Excision was classified as a surgical procedure while other procedure were non-surgical ones. Plastic surgeons were asked if they request a dermatology consultation before treatment decision.

Accuracy was defined as the ability of a test to determine disease correctly by comparison with a reference/gold standard [11]. The accuracy of TD for diagnosis was established by comparison with histopathological examination. Physicians were asked to record their clinical diagnoses after the evaluation of the pictures and clinical information, and then clinical diagnoses were compared with the histological...
diagnoses. TD diagnoses were accepted as correct if they were same with the histopathological diagnoses. The percentage of correct diagnosis was defined as the accuracy of TD. In order to determine the diagnostic accuracy between departments, at least two out of three physicians from the same department were required to make the correct diagnosis.

Dermatologists were asked if they requested to evaluate dermoscopic images of the lesions to confirm their clinical diagnosis made by TD. Regardless of the answer, to determine the effect of TDS on the diagnosis, dermatologists evaluated tele-dermoscopic images of all lesions after clinical images and were asked to make a correct diagnosis, too.

Statistical analyses were performed with the IBM SPSS for Windows Version 23.0. Numerical variables were summarized as mean ± standard deviation or median (minimum-maximum). Categorical variables were given as frequencies and percentages. Categorical variables were compared by chi square or Fisher exact test. Diagnostic accuracy of the physicians were compared by McNemar or Cochran Q test as appropriate. A P value less than 0.05 was considered as significant.

Results

The clinical characteristics of patients and duration, localization, and the histopathological diagnoses of lesions are summarized in Table 1. According to the diagnostic accuracy, there was no statistically significant difference within the physicians of the same department. The P value for dermatologists was 0.41 and for plastic surgeons was 0.07. The percentages of physicians diagnostic accuracy in the same department were demonstrated on Figure 1. The average percentage of diagnostic accuracy among dermatologists was 74.3% and among plastic surgeons was 61.5%. There was not statistically difference in diagnostic accuracy between departments (P = 0.625).

Table 1. Clinical characteristics of patients, features and histopathologic diagnoses of lesions

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>47 (18-83)</td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Duration of lesions</td>
<td></td>
</tr>
<tr>
<td>Since childhood</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>5 (19)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>6 (23)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Localization of lesions</td>
<td></td>
</tr>
<tr>
<td>Scalp</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Face</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>Torso</td>
<td>7 (27)</td>
</tr>
<tr>
<td>The histopathologic diagnoses</td>
<td></td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td>3</td>
</tr>
<tr>
<td>Verruca vulgaris</td>
<td>2</td>
</tr>
<tr>
<td>Epidermal cyst</td>
<td>2</td>
</tr>
<tr>
<td>Dermatofibroma</td>
<td>3</td>
</tr>
<tr>
<td>Fibroma</td>
<td>3</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>1</td>
</tr>
<tr>
<td>Bowen disease</td>
<td>1</td>
</tr>
<tr>
<td>BCC</td>
<td>3</td>
</tr>
<tr>
<td>SCC</td>
<td>3</td>
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</table>

Min = minimum; Max = maximum; BCC = basal cell carcinoma; SCC = squamous cell carcinoma
Dermatologists preferred surgical procedures for 14 (53.8%) lesions and nonsurgical procedures for 12 (46.2%) lesions. Plastic surgeons preferred nonsurgical procedures for one lesion (3.8%) whereas surgical procedures for 25 lesions (96.2%). There was a statistically significant difference between the departments for treatment approaches ($P < 0.001$) (Figure 2).

The need of dermoscopic images in addition to clinical pictures was an average of 80.7% of the lesions for dermatologists. Diagnostic accuracy of TDS was 82% for all lesions which were confirmed by histopathologically. TDS increased the rate of mean diagnostic accuracy of TD from 74.3% to 82% among dermatologists ($P = 0.02$) (Table 2).

Among plastic surgeons, the average percentage of requesting a dermatology consultation before treatment decision was 28.2% (Table 2).

**Conclusions**

In the current digital and locked-down world related to COVID-19 pandemic, TM helps physicians for diagnosis and management of the patients. The diagnostic accuracy and therapeutic approach to NMSLs by using TD was evaluated between dermatology and PRS departments in the current study. While there was no difference between the 2 departments in diagnostic accuracy, a significant difference was found in treatment approach in favor of the surgical approach among plastic surgeons.

Diagnostic reliability and accuracy of TM among dermatologists was found to vary from 47.7% to 88.0% in the literature [2,11,15,19,20]. Fabbrocini et al reported a correct diagnosis rate of 52.0% for dermatologists using TDS for difficult pink lesions [2]. Similarly, in another study, the diagnostic rate of TD was found 59.0% for non-pigmented neoplasms [11]. Şenel et al reported that diagnostic accuracy of non-melanocytic skin tumors by TD was 85.0% and 88.0% for 2 different dermatologists [15]. Diagnostic agreement rates were reported to be between 47.7% to 87.3% for non-pigmented lesions by Warshaw et al [11], Giavina-Bianchi et al also studied diagnostic accuracy of TD for both pigmented and non-pigmented skin lesions. They reported accuracy rates of 75.0%, 71.0%, 64.0% and 50.0% for basal cell carcinoma, squamous cell carcinoma, cysts, and warts/seborrhiec keratoses or lipomas, respectively [20].

Although there are studies which were performed with plastic surgeons about efficacy of TM in various conditions such as wound and burn management, trauma, free flap care, cleft lip/palate repair, there is not any report about diagnostic accuracy of NMSLs diagnosis with TM method [1]. FTF studies demonstrated that the overall diagnostic accuracy of skin lesions for plastic surgeons was around 60.0% to 89.0% [17,21-23]. Clinical diagnosis matched with the pathological diagnosis was considered as a correct diagnosis in these studies. Sönmez et al [17] reported correct diagnosis rate for PRS clinic as 61.4% and Matteucci et al [22] reported an overall diagnostic accuracy of malignant lesions of 83.0%. Basal cell carcinomas were diagnosed with the highest degree of accuracy with 89.0%, whereas squamous cell carcinomas were with a lower level of diagnostic accuracy with 33.0% [22]. The correct diagnostic rate for basal cell carcinoma was 68.0% in the study by Stone et al [21]. In Hallock study, overall diagnostic accuracy was 65% in 2000 excised skin tumors [23]. Our diagnostic accuracy rates for dermatologists and plastic surgeons in the diagnosis of NMSLs were compatible with previous studies.
Figure 2. The frequencies of the treatment approaches of dermatologists and plastic surgeons (p <0.001)

Table 2. The response rates of dermatologists and plastic surgeons

<table>
<thead>
<tr>
<th></th>
<th>D1 n/N (%)</th>
<th>D2 n/N (%)</th>
<th>D3 n/N (%)</th>
<th>Average %</th>
</tr>
</thead>
<tbody>
<tr>
<td>In how many lesions did dermatologists request dermoscopic images to confirm their diagnosis?</td>
<td>24/26 (92.3)</td>
<td>26/26 (100)</td>
<td>13/26 (50)</td>
<td>80.7</td>
</tr>
<tr>
<td>In how many lesions was teledermoscopic pre-diagnosis histopathologically compatible? (Diagnostic accuracy of TDS)</td>
<td>23/26 (88.5)</td>
<td>21/26 (80.8)</td>
<td>20/26 (76.9)</td>
<td>82.0</td>
</tr>
<tr>
<td>For how many lesions that required dermoscopic confirmation were also requested histopathological confirmation?</td>
<td>10/24 (41.7)</td>
<td>17/26 (65.4)</td>
<td>8/13 (61.5)</td>
<td>56.3</td>
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<tr>
<th></th>
<th>P1 n (%)</th>
<th>P2 n (%)</th>
<th>P3 n (%)</th>
<th>Average %</th>
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<tbody>
<tr>
<td>Requesting dermatology consultation</td>
<td>2 (7.7)</td>
<td>11 (42.3)</td>
<td>9 (34.6)</td>
<td>28.2</td>
</tr>
</tbody>
</table>

D1 = Dermatologist-1; D2 = Dermatologist-2; D3 = Dermatologist-3; P1 = Plastic surgeon-1; P2 = Plastic surgeon-2; P3 = Plastic surgeon-3; N = Total number of lesions; ND = total number of lesions that required dermoscopic image; TDS = Tele-dermoscopy

Although there is no data comparing diagnostic accuracy for various skin lesions between dermatologists and plastic surgeons by using TM in the scientific literature, there are some reports with FTF methods [16-18,21]. Sellheyer and Bergfeld reported that dermatologists accurately diagnosed neoplastic and cystic skin lesions nearly 2 times more (75%) than non-dermatologist physicians (40%) or plastic surgeons (45%) [18]. Similarly, Stone et al. reported higher positive predictive value for basal cell carcinoma (as one of malignant NMSLs) diagnosis of dermatologists (85%) than plastic surgeons (68%) [21]. In another study, similar diagnostic rates for basal cell carcinoma were reported among dermatologists and plastic surgeons which were higher than other physicians [16]. In a retrospective study by Sönmez et al, which compared the diagnoses rates for various skin lesions for dermatology and PRS departments, overall correct diagnosis rate of biopsied skin lesions was 64.0% for the dermatology clinic and 61.4% for the PRS clinic and did not differ significantly between the 2 clinics [17]. Similar to the Sönmez et al. study, the diagnostic accuracy rate did not differ between the 2 departments in the current study. Our findings suggest that the TM method has similar results to FTF in terms of comparing diagnostic accuracy for dermatology and PRS departments.

With the use of dermoscopy, correct clinical diagnosis especially for the pigmented lesions and benign neoplastic lesions increased in recent years [17]. The efficacy of contribution of dermoscopy to TD has been investigating recently.
A study evaluating 1000 lesions suggested that TD and TDS might be valid and reliable tools for the diagnosis of actinic keratosis [24]. Additionally, TDS was reported to be superior to FTF dermoscopy and to TD only for detecting early actinic keratoses [24]. Braun et al reported that diagnostic accuracy of NMSLs with TDS was higher than traditional dermoscopic approach with the exception of Kaposi sarcoma [25]. Senel et al reported that TD was a reliable technique for the diagnosis of nonmelanocytic skin tumors and TDS increased the reliability and the accuracy of TD. The accuracy of the diagnoses was significantly increased by the addition of dermoscopic images from 85% to 94% and from 88% to 95% for 2 different tele-dermatologists [15]. On the other hand, it is also reported that TDS had an advantage for only biopsied pigmented lesions [19]. Fabbrocini et al evaluated difficult pink lesions and reported lower correct diagnosis rate for TDS than FTF examination and they discussed that this result might be cause of the absence of typical criteria of pink lesions [2]. In the present study, dermatologists had agreed that TDS was helpful to confirm their clinical diagnoses in 80.7% of the images and TDS increased the mean diagnostic accuracy rate from 74.3% to 82.0% for dermatologists. TD is known to improve diagnostic accuracy and to decrease the rate of unnecessary consultations in dermatology compared with TD alone. In a study about specialists-to-experts store-and-forward TDS, TDS improved diagnostic accuracy of pigmented skin lesions compared with solitary non-expert assessment [26]. Our findings suggest that dermoscopic examination is a frequently used method by dermatologists which increases their diagnostic accuracy on NMSLs diagnosis.

It is in the nature of the profession that surgeons are more prone to surgical approach for diagnosis or management of skin lesions [21,22]. However, some benign skin lesions could be managed non-surgically. Thus, treatment approach between departments was significantly different from each other in the present study, with surgeons more prone to surgical approaches. All these differences of treatment approaches can be related to differences in postgraduate specialization training, indeed.

With increasing technologic advancements, TM holds great potential to augment the dermatologist and plastic surgeon daily practice. Previous studies asserted that the clinical diagnostic accuracy had important outcomes for treatment selection and the prioritization of treatment [22]. Ferrandiz et al reported that teleconsultation before surgery could make an advantage for surgeon to plan the treatment procedure and surgical technique with high diagnostic accuracy rates [27]. Bilgili et al found that diagnostic accuracy was affected positively by a preoperative evaluation by a dermatologist [28]. Travato et al reported that e-consultation for selected plastic surgery patients was an accurate, cost-saving, time-saving technique in the evaluation and management [19]. Matteucci et al emphasized the importance of specializing, especially in lesions with predicted as low malignancy risk [22]. Our results support the idea that e-consultation of the skin lesions to a dermatologist via TM may be an effective method to prevent unnecessary surgery for a plastic surgeon.

Our study had some limitations. There were no predetermined categories for clinical diagnosis of NMSLS and number of lesions was small. With higher number of physicians and different kinds of lesions, requirements of TD between clinics can be determined.

In conclusion, TM is an easy method for NMSLS diagnosis with up to 75% of diagnostic accuracy. Adding TDS to TD increases diagnostic accuracy for dermatologists on NMSLS diagnosis. The difference in treatment approach between departments can be reduced through the effective use of TD and TDS via e-consultation.

References


Elevated Serum Levels of Interleukin-15 in Pemphigus Vulgaris Patients: a Potential Therapeutic Target

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Key words: pemphigus vulgaris, interleukin-15, anti-desmoglein, IL-15, ABSIS


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Pemphigus vulgaris (PV) is a rare autoimmune disease that causes painful blistering. Interleukin-15 (IL-15) as a member of the immunoregulatory cytokines family is associated with the development of the chronic inflammatory or autoimmune disease. There is not much information available in the literature on the exact role IL-15 plays in PV.

Objectives: The goal of this study was to evaluate the serum levels of IL-15 in patients with PV and assess the association of IL-15 with anti-desmoglein antibodies and the severity of the disease.

Methods: Fifty-three individuals affected with active PV and 38 age- and gender-matched healthy controls were participated in this study. Disease severity was assessed using Autoimmune Bullous Skin Disorder Intensity Score (ABSIS). Serum levels of IL-15 (pg/mL) and anti-desmoglein antibodies (Dsg1, 3) were determined.

Results: In the patient group, IL-15 serum levels were statistically higher than those in the control group (3.71 ± 1.5 vs. 0.79 ± 1.03, P < 0.001). A positive correlation was found between serum levels of IL-15 and ABSIS (r = 0.5, P = 0.04). We found no significant correlation between serum concentrations of IL-15 and antibodies (Dsg1 or Dsg3).

Conclusions: An increase in serum level of IL-15 in patients with PV and its relationship with disease severity suggest that this cytokine possibly contributes to the pathogenesis of the disease and targeting IL-15 will likely provide a new insight into the treatment of this disease.
Introduction

Pemphigus vulgaris (PV) is a rare autoimmune disorder that causes painful blisters and erosions on the skin and mucosa [1]. PV is caused by environmental and genetic factors that lead to immunological impairments. Auto-antibodies against desmosomal adhesion proteins of epidermal keratinocytes, desmoglein3 and/or desmoglein 1, lead to the loss of epidermal cell adhesion and development of erosive lesions [1,2]. To date, different cytokines, such as osteopontin, interleukin (IL)-4 and IL-21 have been suggested to be associated with disease pathogenesis and severity [3-5]. These cytokines contribute to rising proinflammatory responses and production of autoantibodies through differentiation of naive T-cells into effector T-cells, increased B-cell responses, and favors a class switch to IgG4. Interfering with the function of them using monoclonal antibodies, such as dupilumab for IL-4/IL-4 receptor could be probably effective in treating some PV patients [6,7]. In contrast, regulatory cytokines, such as TGF-β and IL-35-dependent mechanisms could mediate restoration of self-tolerance, which had been broken in patients with autoimmune diseases [8,9]. However, the role of some less studied cytokines, such as IL-15 has remained controversial. To our best knowledge, 3 studies have assessed the serum levels of IL-15 in PV patients. Two have reported increased serum levels of IL-15 compared to the healthy controls [10-12].

IL-15 is a glycoprotein cytokine produced by multiple cell types including monocytes, macrophages, dendritic cells, fibroblasts, and epithelial cells. It is well known that IL-15 contributes to the survival and proliferation of T-cell [13]. It also increases the proliferation of B lymphocytes and promotes their differentiation into the plasma cells [13,14]. Recent studies have indicated that inhibiting IL-15 with various methods may be the goal of appropriate treatment to reduce inflammation [14].

Objectives

IL-15 is involved in the pathogenesis of a variety of autoimmune diseases such as Sjogren disease, Behcet disease, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [3,15]. There has been little information about the exact role of IL-15 in pemphigus pathogenesis or how IL-15 production relates to the severity of pemphigus.

In this regard, the goal of this study was to assess the serum levels of IL-15 in patients with PV and to find out whether IL-15 levels were associated with severity of their disease.

Methods

Patients

To evaluate the serum levels of IL-15, 53 individuals with active PV and 38 healthy individuals were enrolled in this study. Among 53 patients, 37 cases were newly diagnosed while 16 cases were presented with relapse during minimal therapy (5-10 mg prednisolone per day). PV was diagnosed based on clinical evidence, histopathologic findings, Direct Immune-Fluorescence examination and the detection of serum autoantibodies by ELISA. Participants with any history of inflammatory/autoimmune diseases, hematologic and solid malignancies, viral hepatitis, and HIV were excluded. This study was approved by the ethical committee of our skin research center (ethical code: IR.SBMU.SRC.REC.1395.41). Prior to enrollment in the study, all participants provided written informed consent.

Clinical and Laboratory Data

All the patients enrolled in the study had an active disease, defined as the development of at least 3 de novo blisters/erosions, which do not heal spontaneously within one week. The Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) was used to assess the severity of the disease. The ABSIS provides a maximum score of 206 (150 points for skin involvement, 11 points for oral involvement, and 45 points for subjective oral discomfort) [16]. The score is determined by calculating the percentage of blisters involvement and erosions on the skin, along with weighting factors at the stage of the blistering and erosions, respectively. Discomfort during eating and drinking is also considered [16].

Cytokine Measurements

For evaluating the level of IL-15 and anti-desmogleins (Dsg), 10 ccs venous blood of each participant was collected. The blood samples were centrifuged to gather the sera. Then, the sera were frozen at –80°C. After gathering all the samples, levels of IL-15 were measured by an ELISA kit (Diaclone, France), according to the manufacturer’s instructions. Using the ELISA method (Euroimmun AG) anti-Dsg 1 and 3 antibodies were measured in patients. Values ≥ 20 of relative units per milliliter (RU/ml) were considered positive.

Statistical Analysis

Findings were respectively expressed as mean ± standard deviation or as number (percentage) for continuous variables and categorical data, respectively. Independent samples t test and non-parametric Mann–Whitney U test were applied to compare the means of continuous variables and chi squared test was used for categorical variables. Analysis of variance (ANOVA test) was used for comparing means between variables. To determine if there was a linear relationship between variables, Pearson correlation testing was performed. We used the statistical package of SPSS version 16.0.0. (SPSS Inc.) To analyze the data. The level of significance was considered as P values less than 0.05.
Results

Patient Characteristics
Fifty-three patients with PV (35 females and 18 males) and 38 healthy individuals (24 women and 14 men) were enrolled in the study. The control group was frequency-matched to cases by gender and age. The mean ages of patients and control subjects were equal to 45.62 ± 12.27 and 44.21 ± 13.15, respectively. The baseline demographics and clinical characteristics of the participants have been presented in Table 1. The two groups were comparable in age, gender, and comorbidities (Table 1).

Serum Levels of IL-15
PV patients had significantly higher levels of IL-15 than controls. The mean serum levels of IL-15 ± SD in PV patients were 3.71 ± 1.5 pg/ml, while for healthy controls were 0.79 ± 1.03 pg/ml, which was statistically different (P < 0.001). Figure 1 demonstrates the IL-15 levels in these two groups. In patients with PV, no significant correlations were detected between IL-15 levels and anti-Dsg1 (r = 0.06, P = 0.6) or anti-Dsg3 (r = 0.006, P = 0.9) antibodies. Serum levels of IL-15 were positively correlated with PV severity according to total ABSIS (r = 0.5, P = 0.04).

Conclusions
In this study, we have evaluated plasma levels of IL-15 in patients with PV in the active phase of the disease and searched for a potential relationship between levels of IL-15 and the severity of the disease. We have found that levels of IL-15 are significantly higher in patients compared to healthy controls. Our study group results were comparable to those previously reported [10,11].

Figure 1. Serum IL-15 concentrations (pg/ml) in patients with pemphigus in comparison to healthy controls. Overall, IL-15 levels in the pemphigus group were higher than that of the control group (P < 0.001). IL-15 = Interleukin-15.
Approximately two decades ago, D’auria et al assessed the levels of IL-15 in the serum sample of patients affected with three different bullous dermatoses (5 with bullous pemphigoid, 15 with PV and 15 with pemphigus erythematosus) [10]. They showed a higher level of IL-15 serum in all the dermatosis as compared with healthy subjects. They also showed a significant correlation between the number of lesions and IL-15 serum levels [10]. Additionally, Ameglio et al showed increased levels of interleukin 15 in the serum of 15 PV patients with active disease [11]. In contrast, in a recently conducted study, Timoteo et al revealed a significantly lower serum level of IL-15 in patients with PV than in control group patients [12]. In their study the study population consisted of non-active patients under pharmacologic therapy, then their results can be confounded by potential suppressive effects of immunosuppressants on IL-15 secretions.

IL-15 is assumed to be a member of the immunoregulatory cytokines family which is primarily produced by monocytes, macrophage, dendritic cells, fibroblast, and epithelial cells.

It is believed that IL-15 overexpression is associated with the development of chronic inflammatory disease or autoimmune disorders. When IL-15 is overexpressed, autoreactive T-cells are survived for longer periods of time, that results in abnormal lymphocyte activation [14]. Furthermore IL-15 is also involved in the activation and proliferation of Natural Killer cells (NKs) [17]. Stern et al have suggested a possible role for NKs in the pathobiology of PV and D’auria et al have shown that the number of circulating natural killer cells is significantly correlated with the concentration of IL-15 in patients with pemphigus [10,18].

According to the mentioned role of IL-15 in the differentiation and development of involved cells in immune responses, the role of this cytokine has been studied in a number of autoimmune diseases. There are some reports showing that the mean levels of IL-15 serum are significantly higher in Behcet disease, SLE and rheumatoid arthritis [19]. Active SLE patients had significantly higher levels of IL-15 serum compared to healthy controls, while it was not directly associated with disease activity [20]. The levels of IL-15 in the serum and synovial fluid of patients with rheumatoid arthritis, were much higher compared to the controls [21]. Interestingly, the levels of IL-15 were related to the disease severity and serum levels of IL-15 were strongly correlated with the levels of rheumatoid factor and anti-CCP [21]. Collectively these findings indicated that IL-15 is a key cytokine in several autoimmune diseases, and raises the possibility that targeting IL-15 with various anti-IL-15 approaches

### Table 1. Baseline demographics and clinical characteristics of patients with pemphigus and healthy controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PV patients (N = 53)</th>
<th>Healthy controls (N = 38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35 (66.0% )</td>
<td>24 (63.2% )</td>
<td>0.70</td>
</tr>
<tr>
<td>Male</td>
<td>18 (34.0% )</td>
<td>14 (36.8% )</td>
<td></td>
</tr>
<tr>
<td>Age, Years</td>
<td>45.62 ± 12.27</td>
<td>44.21 ± 13.15</td>
<td>0.60</td>
</tr>
<tr>
<td>Median (range)</td>
<td>46 (21 – 72 )</td>
<td>45.50 (25 – 73)</td>
<td></td>
</tr>
<tr>
<td>Time until diagnosis or exacerbation, month</td>
<td>2.6 ±2.3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Type of pemphigus involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal</td>
<td>18 (34%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>7 (13.2%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Muco-cutaneous</td>
<td>28 (52.8%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>ABSIS, Mean ± SD; Total score a</td>
<td>36.88 ± 24.92</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Anti-Dsg1 Antibody (RU/ml) Mean ± SD</td>
<td>238.68 ± 47.70</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Anti-Dsg3 Antibody (RU/ml) Mean ± SD</td>
<td>729.63 ± 99.05</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>IL-15 (pg/ml) Mean ± SD</td>
<td>3.71 ± 1.5</td>
<td>0.79 ± 1.03</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

ABSIS = Autoimmune Bullous Skin Disorder Intensity Score; Dsg = Desmoglein; IL-15 = Interleukin-15; SD = standard deviation.

Values are reported as numbers (%) unless otherwise specified. *Total score is sum of objective and subjective scores.
may provide a new insight for the treatment of such disorders [19]. For instance, in an animal model of human psoriasis (xenograft mouse), the IL-15 blockade led to the psoriasis resolution [22]. In rat models of induced arthritis, weekly administration of small interfering RNA targeting IL-15 reduces the expression of proinflammatory mediators in the inflamed joints, alleviates disease progression and significantly inhibits the clinical, radiologic and histologic features of rheumatoid arthritis [19].

In the case of pemphigus, corticosteroid medications that usually used to suppress auto-antibodies, include delayed and serious side effects [23]. Targeting B-cell by the anti-CD20 molecule (rituximab) is currently the best available agent for the treatment of pemphigus patients not responding to conventional treatments [24]. This drug eliminates peripheral B-cells. B-cell depletion, may not be desirable because B-cells are essential for antibody production, activation of T-cells and complements. Therefore, interrupting the homing of B-cells by blocking the IL-15 pathway might be a suitable alternative to reduce excessive inflammation [14]. Torn et al showed that in patients with RA, the treatment with rituximab significantly decreased IL-15 serum levels as well as IL-15 cellular levels. They concluded that sustained clinical improvement following rituximab treatment was related to IL-15 and the mechanisms by which IL-15 exerts influence on T-cells [25].

Based on our findings, the elevated levels of IL-15 in sera of patients with pemphigus suggest that this cytokine may actually be involved in pathogenesis of pemphigus. The generalizability of these results is subject to certain limitations. For instance, in our study, we did not analyze the serum level of IL-15 after treatment of patients with steroid pulse or rituximab, and we intend to address it in future work. In our study, although we showed there is a positive correlation between serum IL-15 levels and disease severity we did not find a direct association between IL-15 serum levels and anti-Dsg levels. It might be due to different mechanisms regarding pemphigus pathogenesis and autoantibody production. It could be speculated that IL-15 might rather be involved in tuning the immune system towards autoimmunity not to directly exert its influence on antibody production.

Taken together our findings suggest that levels of IL-15 in the sera of patients with pemphigus are high, which suggests that this cytokine may have a role in the pathogenesis of pemphigus. Whether the higher level of IL-15 is the cause or result of autoimmune diseases remains to be determined in future studies.

Understanding the role of IL-15 in PV provides a scientific basis for the development of novel therapeutic options for this autoimmune disease. Anti-cytokine therapy is an emerging treatment and considered to be a promising therapy in autoimmune diseases; while There is a need for further clarification to establish whether inhibition of IL-15 action might prove valuable in the treatment of PV.

References


Efficacy of a Topical Formulation of Henna (Lawsonia Inermis Linnaeus) on the Itch and Wound Healing in Patients With Epidermolysis Bullosa: a Pilot Single-arm Clinical Trial

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Key words: epidermolysis bullosa, Lawsonia plant, wound healing, pruritus, complementary therapies


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Competing interests: The authors declare that there is conflict of interest, in the way that two individuals listed in authors’ list, MMP and ZP, suffer from DEB and they participated in this clinical trial, but they did not have any role in response evaluation of the drug.

Authorship: Conception and design of the work: MN, MMP, MH, NS, MM, ZP; data collection: MN, NS, MM; analysis and interpretation of the data: MN, MH, MM, NS; statistical analysis: MMP, MM; drafting the manuscript: MN, MMP, NS, MM, ZP; critical revision of the manuscript: MMP, MM, NS, MH, Final approval: MN, MMP, MH, NS, MM, ZP

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ABSTRACT

Introduction: Epidermolysis bullosa (EB) is a rare inherited genetic skin disorder with severe skin itching and recurrent blisters and erosion. There is no effective and specific therapy for all types of EB.

Objectives: The aim of this study was to evaluate a topical formulation of henna (Lawsonia inermis Linnaeaus) in the management of wounds and the itching sensation in patients with EB.

Methods: This is a pilot single-arm clinical trial. Nine patients with recessive dystrophic EB, with the age range of 5 to 32 years were enrolled in the study. The patients were instructed to apply the topical...
Objectives

To the best of our knowledge, there are no studies on the efficacy of henna in the management of wounds and itch in patients with RDEB. The aim of this study was to evaluate the efficacy of henna in the wound healing process and itch-ing complaints in patients with RDEB.

Methods

Study Design

This study was designed as a single-arm, uncontrolled clinical trial. This study was in compliance with the Declaration of Helsinki (1989 revision) [17], and also approved and monitored by the Ethics Committee of Shiraz University of Medical Sciences (License number: IR.SUMS.REC.1398.761). Moreover, the enrolled patients were informed completely about the protocol of the study and signed the written informed consent. The patients were permitted to withdraw from the study at any time of the study. This clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT) by IRCT20150825023753N14 code (http://www.irct.ir/trial/41647).

Sample Size and Study Population

Patients with RDEB were recruited from Faghihi Dermatology Clinic, Shiraz University of Medical Sciences, Shiraz, Iran. Given the rarity of RDEB, the researchers decided to enroll at least seven patients in this pilot study.

Inclusion criteria were patients with RDEB, who signed the written informed consent (themselves or their parents if less than 15 years old) to participate in the study. The exclusion criteria were a positive history of allergic reaction to henna, or glucose-6-phosphate dehydrogenase (G6PD) deficiency, and any other systemic diseases.

Drug Preparation

Henna (Lawsonia Inermis Linnaeus) leaves were gathered from Shahdad fields (Kerman, Iran) and dried. A botanist

Introduction

Inherited epidermolysis bullosa (EB) is a rare genetic skin disorder that can affect many extracutaneous organs including the gastrointestinal and genitourinary system, eye and etc [1,2]. There are four major types of inherited epidermolysis bullosa; epidermolytic (EB simplex [EBS]), lucidolytic (junctional EB [JEB]), dermolytic (dystrophic EB [DEB]), and Kindler syndrome [3]. The common characteristics of all subtypes of EB are recurrent blistering and erosions (after even minor trauma or traction) of skin and the organs covered by mucous membrane [4].

The pathogenesis of EB is the mutation of the genes which is caused due to dysfunction of collagen type VII that is the main component of the anchoring fibrils located below the lamina densa layer of the epidermal basement membrane zone [2]. EB patients, especially patients with recessive dystrophic EB (RDEB), suffer from severe skin itching and also recurrent blisters and erosion [2,5]. There is no specific therapy for all types of EB, therefore supportive care including wound care, control of infection and itching are very important [6]. Using topical and systemic antibiotics, analgesics, antihistamines are very popular in these patients.

Henna (Lawsonia Inermis Linnaeus) is one of the most commonly used medicinal plants in traditional Persian medicine as a treatment for dermatological conditions and improving wound healing [7,8]. There are several studies demonstrating the efficacy of henna on skin disorders such as dermatitis including diaper dermatitis, bedsore, itch, and et. [9-12]. It has been shown that henna can improve the wound healing process and also has antipruritic effects [13,14]. In addition, some investigations revealed the antimicrobial and antifungal properties of henna. These effects are considered to be due to high concentrations of some components in this plant including carbohydrates, anthraquinones, naphthoquinone derivatives, flavonoid, and phenolic components. [15,16].
at Kerman University of Medical Sciences authenticated the plant and recorded it with a specified voucher number (No: KF-1408). The maceration method five times was conducted to prepare the hydro-ethanolic extraction (30:70). The gathered extract was purified through filtration and concentrated by a vacuum rotary evaporator and dried in an oven 40°C. The ointment containing 1% henna was prepared by dissolving a one-gram fine powder of dried henna extract in the minimum volume of ethanol 40%, then it was dispersed in 99 grams of Eucerin through geometric dilution. The prepared ointment was packed in 50-gram containers for delivery to the patients.

Pharmaceutical Properties of the Ointment
The quality control of the prepared ointment was performed according to WHO guideline [18]. Pharmaceutical characterizations of henna ointment were evaluated as follows [19-23]:

Determination of pH
Some ointment was heated up to the melting point and diluted with a 1:9 dilution ratio (1 unit of drug and 9 units of water) and measured with a pH meter. This procedure was repeated three times and its mean and standard deviation were recorded.

Homogeneity
Homogeneity of the herbal ointment was evaluated for any aggregation by the skin test. In this study, 12 healthy volunteers tested some of the product on the back of their hands and were asked to express their satisfaction with the particle being present in the ointment.

Total Polyphenolic Content
The total phenolic content of the extract and ointment were measured based on the Folin-Ciocalteu method.

Rheological Behavior
Cone and Plate Brookfield rheometer (Brookfield Engineering Laboratories) at 25°C was performed to evaluate the rheological behavior of ointment for triplicate.

Spreadability Test
Two horizontal glass plates (10 cm × 10 cm) were conducted to assess the spreadability of the prepared ointment. The spreading diameter of one gram of sample between plates was measured under 25 grams standard weight shear application three times.

In Vitro Drug Release
Two grams of henna ointment were poured into a 10-kDa semi-permeable dialysis membrane bag. After dispersing, it was immersed in 50 ml of 25 mM phosphate buffer solution (PBS) at 37 ± 0.5 °C and rotated at 100 rpm. For 24 hours, at a specified interval, 1 ml volume of PBS solution was sampled and replaced with the same volume of PBS. The samples were analyzed by UV spectrophotometer and repeated three times and the amount of active ingredient release was calculated according to the standard curve.

Microbial Control
The microbial and fungal control tests of the product were performed by Barij Essence® Pharmaceutical company (serial number:1521M98; batch number: 9805101) for aerobic microorganisms, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, modals, and yeasts enumeration.

Intervention and Follow-up of the Patients
The patients were instructed to use a fingertip of henna ointment once a day on two erosions and also on two sites with moderate to severe itching for 4 weeks with first, second, and fourth week follow-up visits. Patient global impression of improvement (PGI-I), visual analog scale (VAS), and clinical global impression of improvement (CGI-I) were used to assess the wound healing process and itching discomfort. Furthermore, photographs were taken of all of the patients.

Furthermore, wound improvement response was defined as excellent (90% improvement), good (50%-90% improvement), mild (20%-50% improvement), and fair (less than 20% or worse) according to general appearance.

At the end of the study, patients or their parents (for children participants) were asked to express their opinions about the efficacy of henna ointment in comparison to other used medications.

Statistical Analysis
Statistical Package for Social Sciences, SPSS version 18 (SPSS Inc.), was used for data analysis. According to the low sample size, Freedman test was used for assessment of the effects of henna ointment on the variables of the study. P value equal to or less than 0.05 was considered significant.

Results
Pharmaceutical Characterization
The measured pH of ointment was 6.4 ± 0.3. This ointment displayed rheological thixotropic behavior. The results of the spreadability test showed that the mean diameter for henna ointment was 9 ± 0.8 cm. Folin-Ciocalteu method was used to determine total phenolic contents in terms of Gallic acid equivalent (GAE) in mg/g of the extract. Based on the equation of the calibration curve (y = 0.007x+0.006, $R^2 = 0.999$), the total phenolic content of the extract and ointment were 129.6 ± 1.1 and 0.98 ± 0.18 mg/g of extract, respectively.
The rate of drug substance release is presented in Table 1. As shown in Figure 1, the release of active ingredients of henna ointment follows the Weibull equation \( Q = 1 - \exp\left(-\frac{t}{\tau}\right)^A \) with \( R^2 = 0.97 \) so that \( \tau \) (time constant) is equal to 6.92 and \( A \) (shape parameter) is equal to 1.03. The prepared product releases half of its active ingredient content up to 4 hours and about 90% of its active ingredient content releases up to 12 hours after application. This release kinetic is consistent with topical products containing ointment-based hydroalcoholic extracts.

**Participants Enrollment and Basic Characteristics**

A detailed description of the patients enrollment and analysis is given in Figure 2. Nine patients were enrolled in the study. Two patients were lost to follow-up. Finally, 7 out of 9 patients including 3 boys and 4 girls completed the study. The age range of the patients was 5-32 years.

**Efficacy Outcomes**

The average drug satisfaction rate was reported 74% (min = 50%, and max = 90%) by the patients. For more details, based on PGI-I, 6 patients reported “very much better” and 1 reported “much better” in itching discomfort after using henna ointment. According to CGI-I, the physician concluded that all the patients were “much better” and “very much better” after using henna ointment. There was a significant improvement in the skin symptoms of epidermolysis bullosa including skin redness, itching, burning, and local warmness sensation \((P < 0.05)\). Local pain decreased during the study period, but this was not statistically significant \((P < 0.19)\) (Table 2). Moreover, Figure 3 shows the photos of 3 patients with RDEB before the treatment and after four weeks of receiving topical 1% henna ointment.

**Qualitative Evaluation of Patients Opinion About Topical Henna Ointment**

Five out of 7 patients who participated in the study reported henna as the most effective ointment for their pruritus in comparison to other medications, including corticosteroids, Vaseline, and repair creams. In addition, most patients had a good experience in wound healing effect while using henna ointment, at least as well as conventional medicine such as Mupirocin, MEBO\textsuperscript{®} and BIAFINE\textsuperscript{®} topical emulsion.

**Side Effects Evaluation**

No serious adverse effect was observed. One patient reported moderate xerosis of skin after continuous application of henna after 4 weeks so that he needed to apply larger amounts of emollient medicines.

**Conclusions**

This study showed that the 1% henna ointment could improve skin redness, itching, burning, and local warmness. But it should be considered that it was a pilot study and further studies with a higher number of cases are necessary to approve these results. Although EB patients suffer from several severe complications related to their disease,
ENROLLMENT

ASSESSED FOR ELIGIBILITY (N=12)

EXCLUDED (3)
- NOT MEETING INCLUSION CRITERIA (N=3)

NOT RANDOMIZED (N=9)

ALLOCATED TO INTERVENTION (N=9)

- RECEIVED ALLOCATED INTERVENTION (N=9)

LOST TO FOLLOW-UP (2 LEAVING CITY) (N=2)

DISCONTINUED INTERVENTION (N=0)

ANALYSÉD (N=7)

- EXCLUDED FROM ANALYSIS (N=0)

Figure 2. TRENDS flow chart of efficacy of a topical formulation of henna (Lawsonia inermis Linnaeus) on the itch and wound healing in patients with epidermolysis bullosa.

Table 2. Mean of dermatological complaints scores from baseline to weeks 1, 2 and 4 in patients with epidermolysis bullosa who were treated with local henna ointment

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Weeks</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 1</td>
</tr>
<tr>
<td>Skin redness (mean ± SD)</td>
<td>6.28 ± 1.26</td>
<td>6.14 ± 1.10</td>
</tr>
<tr>
<td>Itching sensation (mean ± SD)</td>
<td>8.57 ± 0.71</td>
<td>4.71 ± 0.47</td>
</tr>
<tr>
<td>Skin burning (mean ± SD)</td>
<td>3.57 ± 1.21</td>
<td>2.28 ± 0.77</td>
</tr>
<tr>
<td>Local warmness sensation (mean ± SD)</td>
<td>5.14 ± 0.98</td>
<td>4.00 ± 0.92</td>
</tr>
<tr>
<td>Local pain (mean ± SD)</td>
<td>4.71 ± 1.45</td>
<td>4.14 ± 1.24</td>
</tr>
</tbody>
</table>

a. P-value; b. SD = standard deviation

there are not enough randomized clinical trials for novel drugs that can manage their complications.

EB is a non-curable hereditary condition with several cutaneous and extracutaneous manifestations. Skin redness (dermatitis), pruritus, burning sensation in the skin, local warmness sensation, repeated ulceration, and pain are the most common cutaneous manifestations and complaints of patients with EB [24]. These manifestations could affect the quality of life in patients with EB and their families [25,26]. Therefore, most of the time patients, their parents, and health care providers try to administer multiple topical medications including natural and herbal remedies to manage or relieve these symptoms [27].

Henna is one of the herbal medications that is used commonly in both traditional and folk medicine for the treatment of skin, hair, and nail diseases, as well as cosmetic problems [7,28,29]. Niazi et al demonstrated that henna ointment could improve the symptoms of contact dermatitis including skin edema, itching, sweating, skin thinning and pain which is consistent with our study [12]. However, unlike our study,
The mechanisms of wound healing of topical henna are unclear till now, but one recent study suggests that these mechanisms may include reduction of tissue inflammation and increasing cellular glucose uptake, which was mediated by up-regulating the expression of glucose transporter-1 and insulin-like growth factor I. Furthermore, this study showed that topical henna could shorten the inflammatory phase of the wound healing process, accelerate cellular proliferation, raise wound contraction ratio, and caused improvement of revascularization, collagen deposition, and re-epithelialization rate, and promotion of intracytoplasmic carbohydrate storage [34]. According to the knowledge of TPM, “Ghabz”, with nearly meaning of “contraction” in conventional medicine, is the common feature of drugs that are effective in wound healing [35, 36], as well as henna [29, 37], that is in line with the finding of conventional medicine.

The present study showed that 1% of henna ointment had an acceptable effect on skin characteristics in patients with EB. In fact, all the selected wounds of these patients were improved clinically during to first two weeks of the study. Mourad et al demonstrated that the henna gel had a significant effect on wound healing in in-vivo model. The results of this study were confirmed by histological stain assessments [13]. The study of Shiravi et al revealed that henna had anti-inflammatory and anti-bacterial effects in Wistar rats. According to this study, reduction of inflammation, edema, bleeding, and increased collagen formation resulted in acceleration of wound healing, angiogenesis, and vasodilatation in these rats [33].

The mechanisms of wound healing of topical henna are unclear till now, but one recent study suggests that these mechanisms may include reduction of tissue inflammation and increasing cellular glucose uptake, which was mediated by up-regulating the expression of glucose transporter-1 and insulin-like growth factor I. Furthermore, this study showed that topical henna could shorten the inflammatory phase of the wound healing process, accelerate cellular proliferation, raise wound contraction ratio, and caused improvement of revascularization, collagen deposition, and re-epithelialization rate, and promotion of intracytoplasmic carbohydrate storage [34]. According to the knowledge of TPM, “Ghabz”, with nearly meaning of “contraction” in conventional medicine, is the common feature of drugs that are effective in wound healing [35, 36], as well as henna [29, 37], that is in line with the finding of conventional medicine.

The findings of our study showed that topical henna ointment did not relieve pain sensation of the patients with EB. This result may be referred to stimulate pain receptors of the selected sites by pain signals coming from contiguous wounds. This finding was not in line with the other studies. The study of Nesa et al showed remarkable analgesic, anti-inflammatory, and central nervous system (CNS) depressant effects of henna [38]. Hasan Imam et al suggested that the analgesic effect of henna was resulted from alpha

Figure 3. This image shows the patients with recessive dystrophic epidermolysis bullosa (RDEB) who were enrolled in the study before the treatment (A-C) and after four weeks of receiving topical 1% henna ointment (D-F). (A and D) The right knee of a 6-year-old boy with RDEB. (B and E) The left forearm of a 32-year-old girl with RDEB. (C and F) The back of a 10-year-old boy with RDEB.
amylase enzyme inhibitory and Anti-inflammatory effects of this herbal remedy [39]. The difference in the results may be due to different doses and routes of administration. Moreover, previous analgesic effects are reported in animal model, but our study was on human EB subjects with potential different in pain pathways.

One out of seven patients reported that the skin of the areas in contact with the drug had become drier and flakier. According to the best of our knowledge, there are some evidences of skin dryness after using topical henna in literature review. However, it is compatible with side effects reported in traditional Persian medicine for henna.

Other reported side effects for topical use of henna are acute allergic contact dermatitis [40], temporary localized hypertrichosis [41], hair and clothing dye allergy [42], vesicular erythema multiforme-like reaction, [43] and hemolysis in patients with G6PD deficiency [44].

Most of the patients were more satisfied with using henna ointment in comparison with conventional medications, especially in the management of pruritus and inflammation, as well as its wound-healing effects. This is the first study investigating the efficacy of herbal medicine in the management of EB complications. Therefore, it was impossible to compare this product with other herbal remedies in EB. But there is a great piece of evidence showing the efficacy of topical usages in dermatological conditions, such as wound, androgenic alopecia, and prevention and treatment of pressure ulcers, dermatitis, and much more [9,11,45-47].

There were several limitations in this study. First, this was a non-controlled single-arm clinical trial; therefore, the results of this study had not been compared with placebo or other medications. We did not administer a second arm for this trial because there is not any standard and defined treatment for EB ulcers and patients usually apply different or multiple medications for controlling the itching sensation and wound healing with different responses. Second, we used a researcher-made checklist for evaluating the patients. Although the face validity and content validity of this questionnaire were acceptable, we could not evaluate the internal validity of the questioner because of a low sample size of the study. Next, because of the rarity of the disease, the sample size of the study was low. Finally, the age range of the patients was wide (5-32 years); therefore, the parents evaluated the efficacy of the drug for children and this can be a probable confounding factor.

According to the results of this pilot study, the topical formulation of henna may be effective in the management of wound, itching, burning, stringing, and cutaneous warmthness sensation in patients with EB. In this regard, we suggest further controlled clinical trials with larger sample sizes and longer duration of follow-up to evaluate the efficacy of this herbal medication.

References


Facial Dermatoses in Patients With Blepharitis: a Cross-sectional Prospective Analysis

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Key words: facial dermatoses, blepharitis, demodicosis, rosacea, seborrheic dermatitis

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ABSTRACT

Introduction: The relationship between facial dermatoses and blepharitis has been known for a long time.

Objectives: We aimed to investigate the frequency of accompanying facial dermatoses in patients with blepharitis and their relationship with the severity of blepharitis.

Methods: In this cross-sectional study, 95 patients with blepharitis were examined for attending facial dermatoses. The type of blepharitis, the severity of blepharitis, and the degree of dry eye were determined in the patients. Dermoscopic and microscopic examinations were used in the diagnosis of facial dermatoses. The history of allergic rhinitis was questioned because Demodex species frequently accompany blepharitis, facial dermatoses, and allergic rhinitis patients. Mann-Whitney U test was used compare 2 independent groups. In comparing categorical variables, Pearson chi-Squared, Fishere Exact, and Fisher-Freeman-Holton tests were used.

Results: At least 1 facial dermatosis was detected in 84.2% patients, and we did not see any facial dermatosis in 15.8% ones. No patients had acne, which is one of the most common facial dermatoses. The most common facial dermatosis detected in our patients was facial demodicosis (57.9%). It was followed by seborrheic dermatitis (22.1%) and rosacea (12.6%), respectively. In addition, 2.1% of the patients had atopic eyelid dermatitis, 23.2% had a history of allergic rhinitis, and 63.2% had ocular demodicosis.

Conclusions: It is essential to perform dermatological examinations of all patients with blepharitis in terms of accompanying facial dermatoses and their early diagnosis.
Introduction

Blepharitis is a multifactorial inflammatory condition of the eyelids that occurs in less than 1% of the general population. It is classified as anterior blepharitis and posterior blepharitis according to the eyelash margin of the affected area. Affected individuals may complain of irritation as eyelid itching, burning sensation, watering-epiphora, eyelid crusting, foreign-body sensation, a feeling of heavy eyelids, and photophobia and blurring vision. Rarely blepharitis may lead to keratopathy, corneal ulceration, permanent changes of eyelid morphology, and result in decreased vision. Blepharitis is commonly categorized by anatomical location. Anterior blepharitis may occur in seborrheic or non-seborrheic types and is associated with increased eyelid commensals such as Staphylococcus epidermidis and Staphylococcus aureus [1,2].

However, posterior blepharitis is secondary to structural changes and occlusion of the meibomian gland orifices [2,3]. Blepharitis generally occurs due to underlying skin diseases such as seborrheic dermatitis (SD), atopic dermatitis (AD), rosacea, or facial demodicosis (FD) [2,4,5].

In anterior blepharitis, bacterial antigen, exotoxins, and delayed cell-mediated immune hypersensitivity leading to an inflammatory cascade. Infectious blepharitis is characterized by hyperemia, edema, scaling, and telangiectasia of the anterior lid margin. Severe cases are complicated with poliosis, madarosis, eyelid hypertrophy, and corneal scars. Recurrent hordeola are often related to staphylococcal strains in infectious blepharitis [6].

In posterior blepharitis cases, inflammation of the posterior lid margin induces Meibomian gland dysfunction (MGD). Terminal duct obstruction due to hyperkeratinization reduces glandular secretion and causes tear film abnormalities. Evaporative tear disorders are mostly seen in patients with MGD and are reasons for patients complaints [7].

Seborrheic blepharitis more effecting sebaceous gland Zeis than meibomian glands has less inflammation than staphylococcal blepharitis but is characterized by more oily scaling. Some patients with seborrheic blepharitis show MGD [8].

Ocular complications such as eyelid dermatitis, blepharitis, conjunctivitis, cataract, keratoconus are seen in patients with atop dermatitis [2,9]. In the report of the North American contact dermatitis study group, the frequency of atop eyelid dermatitis was reported to be around 13% [10]. Every patient with blepharitis and conjunctivitis should be questioned about the history of atopy. Because it is common in these patients [11].

Rosacea is a progressive facial inflammatory dermatosis that may be associated with systemic diseases. Ocular surface changes such as blepharitis and conjunctivitis are seen in patients with rosacea [12,13].

The parasitic infection Demodex blepharitis is a chronic inflammatory disease caused by Demodex mites, affecting the eyelid margin and ocular surface. The worldwide incidence of ocular Demodex infestation is around 13%-70%. In addition, the presence of Demodex in the eyelashes of 18% of healthy individuals in the 2nd and 3rd decades is reported [5,14]. The rate of Demodex infestation increases with age and is seen in almost all people over 70 years of age [13,15-17].

Demodex mites have also been hypothesized to play a role in the etiology of posterior blepharitis [18]. Infestation along the posterior margin is a reason for obstruction of gland orifices [15]. Demodex’s nutritional source is follicular and glandular epithelial cell sebum [19]. Demodex folliculorum infestation causes anterior blepharitis. Mites deposit their eggs on the base of the eyelashes, and keratin and epithelial cell deposits accumulate, forming cylindrical dandruff, the pathognomonic sign of demodicosis. Mites are in clusters around eyelashes and skin [20,21]. Demodex brevis penetrate the meibomian glands causing gland obstruction and dysfunction inducing marginal blepharitis. They are seen one by one in glands [21,22].

Demodex species are also a common etiological factor for AR and blepharitis. The frequency of facial Demodex, which is thought to be a facilitating factor in patients with AR, was found to be 40% on average [5, 3,24].

Dermoscopy is a good diagnostic tool in common facial dermatoses. Demodex tails and Demodex follicular openings are frequently observed in facial demodicosis. Dotted vessels and fine yellowish scales in seborrheic dermatitis, linear veins in a polygonal network, and follicular pustules in rosacea are diagnostic clues [25].

Objectives

We planned this study to investigate the frequency of SD, AD, rosacea, and demodicosis, which are skin diseases that frequently affect the face and are thought to play an essential role in the etiology of blepharitis. We hypothesized that performing dermatological examinations of all patients with chronic blepharitis may be necessary for the early diagnosis and treatment of facial dermatoses.

Methods

The local ethics committee reviewed and approved the study (protocol ID: 2021/900/88), and written informed consent was obtained from all participants. The study was carried out according to the principles in the Declaration of Helsinki.

Patient Selection and Procedures

A total of 95 patients diagnosed with chronic blepharitis in our ophthalmology clinic and undergoing dermatological
evaluation on the same day were included in the study. The patients were examined for facial dermatoses, and a dermoscopic examination was performed. The history of allergic rhinitis was questioned because Demodex species frequently accompany blepharitis, facial dermatoses, and allergic rhinitis patients. In terms of accompanying demodicosis, skin scraping, standardized skin surface biopsy (SSSB), and eyelash sampling were performed. The duration of blepharitis and facial dermatoses, and the history of allergic rhinitis, were recorded.

**Dermoscopic Evaluation**

The dermoscopic evaluation was performed by using a handheld dermoscope (DermLite DL200HR; 3Gen, Inc.) at \( \times 10 \) magnification (polarized light). Images were recorded directly by the smartphones attached magnetically to the dermoscope. We performed dermoscopic examination with two methods. First, we performed a classical dermoscopic examination (Figure 1, A,B,C). In this method, we placed the dermoscope probe vertically on the cheek skin. Second, our new lateral dermoscopic technique; makes demodex tails more prominent. We put the dermoscope horizontally on the cheek skin and then examined it by pinching between the index finger and the dermoscope (Figure 1, D,E,F, Figure 2).

**Microscopic Eyelid Demodex Examination**

Three eyelashes were taken from the eyelids of both eyes, prepared by glycerine-type separation, and evaluated under a light microscope (Olympus,) at \( \times 40 \) and \( \times 100 \) magnification. At least 3 Demodex folliculorum in each eyelash was considered as Demodex infestation (Figure 3) [26].

**Evaluation of Tear Production**

The Schirmer test was used to evaluate tear production in patients. Test strips were designated “L” and “R” for the left and right eyes, respectively. Afterward, each strip was bent at a 90-degree angle. The patient was told to look up, and the lower eyelid of the patient was pulled down. The curved end of the test strip was placed between the palpebral conjunctiva and the bulbar conjunctiva. This procedure was also done for the other eye. After both strips were seated, the patient was asked to close their eyes for five minutes gently. After five minutes, the test strips were removed. A score of more than 10 mm was considered normal. A score between 5mm and 10mm was graded as mild insufficiency, and a score of less than 5mm was graded as severe insufficiency [27].

**Evaluation of the Severity of Seborrheic Dermatitis**

The Seborrheic Dermatitis Area and Severity Index (SEDASI) scale developed by Micali et al. were used to assess the severity of seborrheic dermatitis [28].

**Demodicosis Classification and Evaluation of the Density of Facial Demodex**

Demodicosis was classified as follows: rosacea-like demodicosis, pityriasis folliculorum, Demodex dermatitis, spinulosis of the face, and pustular folliculitis [29]. Skin samples were taken from the right cheek of the patients using the SSSB method. A microscope slide with cyanoacrylate adhesive is pressed onto the lesion. After 30 seconds, the sample was removed from the skin. The sample was covered with a coverslip and examined by light microscopy at \( \times 10, \times 40 \), and \( \times 100 \) magnification in immersion oil. The total number of viable parasites in a sample was used to assess Facial Demodex severity and density (FDS): 0-5 per \( \text{cm}^2 \), 1+ density, 5-10 per \( \text{cm}^2 \), 2+, 10-15 per \( \text{cm}^2 \), 3+, 15-20 per \( \text{cm}^2 \), 4+ and >20.5 per \( \text{cm}^2 \) was classified as 5+ [30].

**Rosacea Classification and Evaluation of the Clinical Severity (RCS)**

The classification and scoring system of the American National Rosacea Society (NRS) was used for the type and severity of rosacea [31].

**Blepharite Classification and Scoring of Severity**

The Uludağ Ocular Demodicosis Clinical Scoring system (UODS) was used to evaluate the severity of blepharitis. According to this score, if there is at least one stinging, burning, itching, and pain complaint, 1 point is given; otherwise, 0 points were awarded. A score of 1 was given for anterior or posterior blepharitis, and 2 points were given if both were present. One point for long-term use of drops containing preservatives (eg glaucoma drugs); 2 points were given if there was a systemic or local disease other than blepharitis that would cause dry eye. It was given 1 point if there was an epithelial defect and 2 points if it presented with keratitis. The presence of cylindrical dandruff was given 2 points [32].

**Statistical Analysis**

The SPSS 25.0 (IBM Corporation) program was used in the analysis of the variables. The conformity of univariate data to normal distribution was evaluated with the Shapiro-Wilk Francia test, while homogeneity of variance was assessed with the Levene test.

The Mann-Whitney U test was used together with Monte Carlo results to compare two independent groups with each other according to quantitative data. In the comparison of more than two groups according to quantitative data, Kruskal-Wallis H test and Jonckheere-Terpstra test were used together with Monte Carlo results, and Dunn and Tukey tests were used for post-hoc analyses. Kendall tau-b and Spearman rho tests were used to examining the correlations of the variables with each other.
Figure 1. Dermoscopic findings of facial demodicosis (FD). (A) Pityriasis folliculorum on the right cheek area of a young man. The white yellowish structures are Demodex tails (arrows). (B) Cheek area of middle-aged woman. The white yellowish structures are Demodex tails (arrows), and Demodex follicular openings (black circles) are seen. Reticular dilated vessels are remarkable in the patient with a history of intermittent steroidal cream use. (C) Diffuse eyelash demodicosis in an elderly man; white yellowish structures are Demodex tails (arrows); increased vascularity less pronounced possibly due to age-related atrophy. (D and E) Dermoscopy of the cheek region of 2 different patients, lateral dermoscopic examination technique. In the patient on the left, Demodex follicular openings (black circles) and reticular dilated vessels are observed in addition to Demodex tails (arrows). (F) Lateral dermoscopic technique for FD.
Figure 2. Dermoscopic findings of seborrheic dermatitis (SD). (A) Interfollicular pale erythema (red circle) and oily scale (black circle) in the scalp region. (B) Oily scale on eyebrows (circle) (C) Eyelash of the patient with SD. Thin scales (white circles) attached to the eyelashes are seen (no accompanying Demodex). (D) Eyelash demodicosis in a patient with SD. The white yellowish structures are Demodex tails (arrows), and dilated, and arborized vessels are visible. (E) A dermoscopic view of the nasolabial fold. Fine white nonspecific scales are seen (circles). (F) Dermoscopic view of the cheek of a patient with SD accompanied by facial demodicosis. Demodex follicular openings (circles) and Demodex tails (arrows) are visible.
In comparing categorical variables, Pearson chi-Squared, Fisher exact, and Fisher-Freeman-Holton tests were tested with the Monte Carlo simulation technique, and column ratios were compared with each other and expressed according to Benjamini-Hochberg corrected P value results.

Quantitative variables were expressed as mean (± standard deviation), median (minimum/maximum), and median (percentile 25° / percentile 75°) in the tables, while categorical variables were shown as N (%). The variables were analyzed at 95% confidence level, and a P value less than 0.05 was considered significant.

Results

Demographic Data
Thirty-two (33.7%) of our patients were males, and 68 (66.3%) were female. The mean age of our patients was 46.58 (±14.78) years. The mean disease duration was 24.99 (±22.49) months. Ninety-one (95.8%) patients had anterior blepharitis, 22 (23.2%) had posterior blepharitis, and 18 (18.9%) had compound blepharitis. The mean UODS were 4.23 (±2.39). All our patients had at least 1 of the symptoms of eyelid itching, burning sensation, watering, eyelid crusting, feeling of heavy eyelids, and photophobia. We did not find keratitis in any of the patients (Table 1).

The mean Schirmer test values of the patients were 9.46 for the right eye and 9.77 for the left eye, and more than one-third of them had a severe dry eye (Table 1).

At least one facial dermatosis was detected in 84.2% of our patients, and we did not see any facial dermatosis in 15.8%. And none of our patients had acne, which is one of the most common facial dermatoses. The most common facial dermatosis detected in our patients was FD (57.9%). This was followed by SD (22.1%) and rosacea (12.6%), respectively. In addition, 2.1% of the patients had atopic eyelid dermatitis (AED), 23.2% had a history

Figure 3. The appearance of eyelid and eyelashes of a patient with atopic eyelid dermatitis and allergic rhinoconjunctivitis; microscopic views of facial and ocular demodicosis. (A) A middle-aged man with atopic eyelid dermatitis, presumably secondary to scratching trauma. Prominent skin lines (red circle) and polypoid structures (black circles) are seen. (B) Eyelashes of the patient with allergic rhinoconjunctivitis. The white yellowish structures are Demodex tails (arrows). Thin white scales wrapped around the lashes are also observed (circles). (C) Microscopic view of Demodex folliculorum (black circles) and its larvae (red circles) appear on standardized skin surface biopsy (SSSB) (×40). (D) Microscopic view of the eyelash: Demodex folliculorum eggs (black circle) and larvae (red circle) (×40).
Table 1. Blepharitis types and severity, Schirmer scores, facial dermatoses types, rates and severity, together with demographic data in our patients

<table>
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<tr>
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<tr>
<td>Female</td>
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<td>mild</td>
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<tr>
<td>moderate</td>
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<td>Positive eyelash microscopy for Demodex</td>
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<tr>
<td>Ocular demodicosis</td>
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<tr>
<td>Blepharitis duration (m)</td>
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<td>UODS</td>
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<td>Seborrhoeic dermatitis duration (m)</td>
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<td>SEDASI</td>
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<td>Rosacea duration (m)</td>
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<td>Allergic rhinitis duration (m)</td>
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<td>Schirmer right eye</td>
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<td>Schirmer left eye</td>
<td>95 10 (5 / 20)</td>
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m = month; SD = Standard Deviation; SEDASI: Seborrhoeic Dermatitis Area and Severity Index; UODS = Uludağ Ocular Demodicosis Clinical Scoring system.
of allergic rhinitis (AR), and 63.2% had ocular demodicosis (OD) (Table 1).

Duration and Severity of Detected Facial Dermatoses
The patients had not previously applied to the dermatology outpatient clinic regarding this condition, and they had no complaints about this. Therefore, we could not calculate the FD time. The FDS was as follows: + in 4 patients (4.2%), ++ in 5 patients (5.3%), +++ in 16 patients (16.8%), ++++ in 24 patients (25.3%), 6 patients (6.3%) ++++ FD was present. The mean SD duration was 85.71 (±44.79) months. The mean SEDASI was 14.48 (±5.06). The mean disease duration of the patients with rosacea was 41.86 (±13.18) months, and the mean RCS was 7.29 (±1.54) (Table 1).

Relationships Between Duration and Severity of Blepharitis and Duration and Severity of Facial Dermatosis
There was no correlation between blepharitis duration, rosacea duration, SD duration, RCS score, SEDASI scores with blepharitis severity (UODS) in our patients. There was only a weak positive correlation between rosacea duration and UODS and between FDS score and UODS (P = 0.002 and P = 0.013, respectively) (Table 2).

Facial Dermatoses and History of Allergic Rhinitis Compared with the Severity of Blepharitis and Degree of Dry Eye.
In terms of the severity of blepharitis, the median value of the UODS score in the FD group was greater than the median value of the allergic rhinitis group (P = 0.026) and the median value of the SD group (P = 0.001), and it was statistically significant. There was no significant difference in the severity of blepharitis between patients with allergic rhinitis and patients with SD (P = 0.208). No significant correlation was found between patients with allergic rhinitis and patients with SD in terms of dry eye degree (P > 0.05) (Table 3).

However, there was a weak positive correlation between the presence of FD with Schirmer scores of the right and left eyes (r = 0.369 and 0.489, respectively), which was statistically significant (P = 0.027 and 0.002, respectively) (Table 4).

Anterior blepharitis was significantly higher in the FD group than in the SD and AR groups (P = 0.028) (Table 5).

We examined the rate of FD in facial dermatoses we detected. We observed a higher rate of FD, especially in patients with rosacea compared to other groups. FD was present in 66.7% of patients with rosacea and 47.6% of patients with SD. We found the incidence of FD to be quite low (22.7%) in patients with AR than in patients without AR. This difference was statistically significant (P < 0.001). We did not find a significant difference in the incidence of FD in patients with or without SD and with or without rosacea (respectively P = 0.280 and P = 0.510) (Table 6).

Table 2. Relationships between duration and severity of facial dermatosis with blepharitis severity.

<table>
<thead>
<tr>
<th>UODS</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDS</td>
<td>0.255</td>
<td>0.013</td>
</tr>
<tr>
<td>RCS</td>
<td>0.149</td>
<td>0.566</td>
</tr>
<tr>
<td>SD duration</td>
<td>0.262</td>
<td>0.148</td>
</tr>
<tr>
<td>SEDASI</td>
<td>0.275</td>
<td>0.133</td>
</tr>
<tr>
<td>Rosacea duration</td>
<td>0.706</td>
<td>0.002</td>
</tr>
<tr>
<td>Allergic rhinitis duration</td>
<td>0.111</td>
<td>0.518</td>
</tr>
</tbody>
</table>

Kendall tau b test, Spearman rho test. FDS = facial demodicosis severity; r = Correlation Coefficient; RCS = Rosacea clinical severity; SD = seborrheic dermatitis; SEDASI = Seborrheic Dermatitis Area and Severity Index; UODS = Uludağ Ocular Demodicosis Clinical Scoring system.

Table 3. Relationships between facial dermatoses and history of allergic rhinitis with the severity of blepharitis.

<table>
<thead>
<tr>
<th>UODS</th>
<th>Median (q1 / q3)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis (A)</td>
<td>3 (2 / 4)</td>
<td>P (A-B) = 0.208</td>
</tr>
<tr>
<td>Seborrheic dermatitis (B)</td>
<td>2 (2 / 3)</td>
<td>P(A-C) = 0.026</td>
</tr>
<tr>
<td>Facial demodicosis (C)</td>
<td>4 (4 / 5)</td>
<td>P(B-C) = 0.001</td>
</tr>
</tbody>
</table>

Kruskal-Wallis H test (Monte Carlo); Post Hoc test: Dun test.
AR = allergic rhinitis; FD = facial demodicosis; q1 = 25’ percentile; q3 = 75’ percentile; SD = seborrheic dermatitis; UODS = Uludağ Ocular Demodicosis Clinical Scoring System Blepharitis severity score.
Table 4. Relationships between facial dermatosis and history of allergic rhinitis, with the degree of dry eye.

<table>
<thead>
<tr>
<th></th>
<th>Allergic Rhinitis</th>
<th>Seborrheic Dermatitis</th>
<th>Facial Demodicosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Schirmer right eye score</td>
<td>-0.204</td>
<td>0.466</td>
<td>0.324</td>
</tr>
<tr>
<td>Schirmer left eye score</td>
<td>-0.312</td>
<td>0.257</td>
<td>0.324</td>
</tr>
<tr>
<td>SEDASI</td>
<td>-</td>
<td>-</td>
<td>0.106</td>
</tr>
<tr>
<td>FDS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

FDS = facial demodicosis severity; r = Spearman rho test correlation coefficient; SEDASI = Seborrheic Dermatitis Area and Severity Index.

Table 5. The relationship between blepharitis type and severity parameters and facial dermatoses.

<table>
<thead>
<tr>
<th></th>
<th>Allergic Rhinitis (N = 15)</th>
<th>Seborrheic Dermatitis (N = 11)</th>
<th>Facial Demodicosis (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Anterior blepharitis</td>
<td>0.028</td>
<td>0.545</td>
<td>0.280</td>
</tr>
<tr>
<td>None</td>
<td>2 (13.3)</td>
<td>2 (18.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (86.7)</td>
<td>9 (81.8)</td>
<td>36 (100.0)</td>
</tr>
<tr>
<td>Posterior blepharitis</td>
<td>0.545</td>
<td>0.280</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10 (66.7)</td>
<td>9 (81.8)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (33.3)</td>
<td>2 (18.2)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Compound blepharitis</td>
<td>0.280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (80.0)</td>
<td>11 (100.0)</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (20.0)</td>
<td>0 (0.0)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Cylindric scale</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>12 (80.0)</td>
<td>10 (90.9)</td>
<td>9 (25.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (20.0)</td>
<td>1 (9.1)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Droplet usage</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>9 (60.0)</td>
<td>11 (100.0)</td>
<td>31 (86.1)</td>
</tr>
<tr>
<td>Yes</td>
<td>6 (40.0)</td>
<td>1 (9.1)</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Different xerophthalmia cause</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>None</td>
<td>15 (100.0)</td>
<td>11 (100.0)</td>
<td>36 (100.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Epithelial defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (100.0)</td>
<td>11 (100.0)</td>
<td>32 (88.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (11.1)</td>
</tr>
</tbody>
</table>

Fisher freeman Halton test (Monte Carlo). A expresses significance according to AR group, B expresses significance according to SD group, C expresses significance according to FD group, AB expresses significance according to AR and SD group, AC expresses significance according to SD and FD group.

Table 6. Frequency of facial demodicosis in facial dermatoses and patients with allergic rhinitis.

<table>
<thead>
<tr>
<th></th>
<th>Seborrheic Dermatitis</th>
<th>Allergic Rhinitis</th>
<th>Rosacea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Facial Demodicosis</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>None</td>
<td>29 (39.2)</td>
<td>11 (52.4)</td>
<td>23 (31.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>45 (60.8)</td>
<td>10 (47.6)</td>
<td>50 (68.5)</td>
</tr>
<tr>
<td>P</td>
<td>0.280 a</td>
<td>&lt;0.001 a</td>
<td>0.510 a</td>
</tr>
</tbody>
</table>

a: Pearson Chi-Square Test (Monte Carlo).
Conclusions

This study aimed to investigate the frequency of accompanying facial dermatoses in patients with blepharitis and whether there is a relationship between the severity of dermatoses and the severity of blepharitis. As a result of our research, we found that patients with blepharitis mostly have facial inflammatory dermatosis.

We detected at least one facial dermatosis in most of our wastes. This may suggest that a common factor plays a role in the etiopathogenesis of facial dermatoses and blepharitis. For example, many studies suggest that Demodex infestation, which plays a role in the etiology of facial dermatoses, is associated with rosacea and SD [16,33,34].

A similar immunopathogenesis in these disease groups may also be responsible for the association of facial dermatoses and blepharitis. The presence of STAT-1 gene mutations that cause a primary immunodeficiency, which is blamed especially in the etiology of rosacea, Demodicosis, blepharitis, or the emergence of Demodicosis, SD and rosacea in secondary immunodeficiency cases may be a consociate etiopathogenetic factor [35-38].

We thought that the treatment of blepharitis might be triggering facial dermatoses due to the coexistence of facial dermatoses and blepharitis. However, we found the duration of facial dermatosis to be much longer than the duration of blepharitis. For example, as the duration of rosacea increased, the severity of blepharitis increased (P = 0.002). Therefore, blepharitis may actually develop as a result of a chronic facial inflammatory process. We think that the duration of FD is also long in our patients, but prospective studies are needed to explain this.

Both the severity of blepharitis and the degree of dry eye were higher in patients with FD compared to patients with SD and AR. The association of ocular Demodex infestation with dry eye is known [39,40]. This may be related to the presence of OD in the vast majority (85.5%) of our patients with FD, and thus our study supported the presence of dry eye symptoms in patients with OD.

Some patients with blepharitis have a history of AR. Patients with AR also have Demodex infestation. It raises the question of whether there is a cross immune response between house mites and Demodex. However, no allergen cross-reactivity was detected between house dust mites and Demodex [41]. However, we did not associate the development of blepharitis in AR patients with Demodex because only one (6.7%) of our patients with AR had OD. Further clinical studies are needed to explain blepharitis and allergic rhinitis association.

We interpreted the reasons why we found anterior blepharitis more than posterior and compound blepharitis in the FD, SD, and AR groups. We detected cylindric scales in 80% of patients with OD. Since this finding is often associated with *D. folliculorum*, which causes anterior blepharitis, we may have seen anterior blepharitis possibly related to *D. folliculorum* much more in our patients with OD [15, 20, 21]. Since SD involves the Zeis glands more frequently, and anterior segment findings can be expected [8]. Therefore, we may have seen anterior blepharitis more frequently in our SD patients, as expected.

Main limitations of the study were that the information about the drugs used by the patients for blepharitis and their other diseases was not recorded and the lack of a control group.

We detected high rates of facial dermatosis in patients with blepharitis. For this reason, we think that it is essential for all patients diagnosed with blepharitis to be examined in dermatology clinics for facial dermatoses. Thus, we predict that the patient’s quality of life will increase with the treatment of an early-detected facial dermatosis. Furthermore, we are becoming more and more aware that dermatoscopy can be a helpful tool in the diagnosis of periocular diseases besides all skin diseases and facial dermatoses.

References


Application of an Interactive Diagnosis Ranking Algorithm in a Simulated Vignette-based Environment for General Dermatology

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Key words: logic, diagnosis, algorithm, ranking, human-computer interaction


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Diagnostic algorithms may reduce noise and bias and improve interrater agreement of clinical decisions. In a practical sense, algorithms may serve as alternatives to specialist consultations or decision support in store-and-forward tele-dermatology. It is, however, unknown how dermatologists interact with algorithms based on questionnaires.

Objectives: To evaluate the performance of a questionnaire-based diagnostic algorithm when applied by users with different expertise.

Methods: We created 58 virtual test cases covering common dermatologic diseases and asked five raters with different expertise to complete a predefined clinical questionnaire, which served as input for a disease ranking algorithm. We compared the ranks of the correct diagnosis between users, analyzed the similarity between inputs of different users, and explored the impact of different parts of the questionnaire on the final ranking.

Results: When applied by a board-certified dermatologist, the algorithm top-ranked the correct diagnosis in the majority of cases (median rank 1; interquartile range: 1.0; mean reciprocal rank 0.757). The median rank of the correct diagnosis was significantly lower when the algorithm was applied by four dermatology residents (median rank 2-5, P < 0.01). The lowest similarity between inputs of the residents and the board-certified dermatologist was found for questions regarding morphology. Sensitivity analysis showed the highest deterioration in performance after omission of information on morphology and anatomic site.
Introduction

Skin diseases have a profound impact on public health as they are estimated to account for a large fraction of all primary care visits [1,2]. Skin diseases are the fourth most common form of illness and affect almost one-third of the world population at any time [3,4]. Furthermore, because of the rising incidence of skin cancer in most countries, accurate diagnosis and treatment of cutaneous neoplasms are required to maintain a high standard of care in the future. Recent developments in the field of artificial intelligence (AI) propelled machine learning algorithms in the center of image-based diagnostic dermatology [5,6], but this development was also the target of substantial critique [7-9]. The main points of critique include lack of robustness and interpretability of current machine learning algorithms as well as failure to include relevant diagnostic information beyond what is captured in images. A more complete view of the patient including contextual information may lead to better and more robust diagnoses for neoplastic and inflammatory diseases [10,11]. Attempts to incorporate multimodal information in machine learning models for automated diagnosis are emerging slowly [12-17]. Only a few digital tools employ a bottom-up approach starting with the description of the appearance and distribution of primary lesions and additional symptoms [18,19].

Objectives

We recently described an interactive diagnosis ranking algorithm based on high-level, symbolic representations of structured descriptions of dermatologic conditions by human readers [20]. Herein, we want to assess this algorithm in a vignette-based study simulating a potential application in tele-dermatology decision support. The major goals of this pilot study were to assess the baseline performance of such an algorithm and to explore typical problems of human-computer interaction.

Methods

A reasoning-based clinical diagnosis-ranking algorithm (CDRA) was used as an example for an interactive diagnostic system based on high-level, human-readable, symbolic logic [20]. Five physicians with varying experience in clinical dermatology independently rated 58 consecutive patient vignettes (virtual test cases). The raters consisted of structured descriptions of the dermatologic conditions presented in the vignettes. The descriptions were entered into the software via a simple multiple-choice questionnaire, resulting in ranked lists of differential diagnoses.

Clinical diagnostic ranking algorithm

The CDRA uses a custom dermatological knowledge database, containing 620 different dermatologic diagnoses at the time of conducting the study, as described recently [20]. Briefly, it provides probability-ranked differential diagnoses through a reasoning component, based on computational logic. The user interface in this study was a simple questionnaire that allowed users to enter the following information: 1) basic epidemiologic information (patient sex, age, skin type, number of lesions); 2) arrangement of lesion(s) (information regarding multiplicity, distribution and arrangement of the lesions); 3) localization of lesion/s in anatomic areas (including special sites such as sun-exposed areas); 4) morphology of lesion(s); 5) color of lesions; 6) timing and onset of the disease; 7) additional non-cutaneous signs and symptoms. The participants did not receive any additional information or exemplar cases of primary lesions. After completing the input, the algorithm creates a ranked list of all 620 diagnoses in the background. The software generates up to 8 “top-ranked” diagnoses and an arbitrary number of “excluded diagnosis”. No correction of data entry after the first submission was permitted or possible, and users did not see ranked lists at any point.

Rater characteristics and training

Four dermatologists-in-training and 1 board-certified dermatologist from a single center served as independent raters (Supplementary Table 1). Dermatologists-in-training were ranked by post-graduate years (PGY-1 to PGY-4). Before entering any study-specific information, all raters were trained on the technical data entry process of the software. Raters received individual user access for the software and a pdf-file containing all virtual patients in random order. Every rater had a separate computer workstation and no time constraints for entering the information into the CDRA.
Vignettes

The convenience sample was collected from educational material of the Medical University of Vienna, and contained 58 virtual patient cases including common dermatologic diseases but also more rare conditions, if they seemed relevant for a primary care setting. Fitzpatrick skin types, as assessed by a single author based on digital images, were 93.1% I-II (N = 54), 5.2% III-IV (N = 3), and 1.7% V-VI (N = 1). A complete list of diagnoses alongside basic patient information is shown in Supplementary Table 2. Vignettes included a brief medical history covering only the main points, and between one and four representative clinical images involving overviews of different body parts and, if necessary, close-up images of individual skin lesions. The views were selected to allow evaluation of morphologic features of the primary lesions as well as their distribution, arrangement and color. The 58 vignettes covered a range of different disease categories including allergic, autoimmune, benign neoplastic, exogenous, hereditary, infections, inflammatory, malignant neoplastic, and other diseases like melasma or amyloidosis.

Of the 58 vignettes, 31 contained information about non-cutaneous signs and symptoms.

Statistical analysis

A single correct diagnosis served as the ground truth for each vignette. We used the median correct ranking position and the Mean Reciprocal Rank (MRR) to estimate the ranking ability of the algorithm. The Reciprocal Rank is defined as 1/k, where k is the rank position of the correct diagnosis as predicted by the CDRA. The MRR is the mean across all cases. We calculated the Sørensen-Dice-coefficient (Dice) to measure the similarity between descriptions. Paired comparisons of rank positions were performed with the Wilcoxon Signed-Rank test. Confidence intervals (CI) and interquartile range (IQR) are reported where applicable. We used R Statistics (version 4.1.0) for all statistical analyses and applied a Bonferroni-Holm correction to all p-values [21,22]. A two-sided P value < 0.05 indicates statistical significance. Plots were created using ggplot2 [23].

<table>
<thead>
<tr>
<th>Rater</th>
<th>Median Rank Position of the Correct Diagnosis</th>
<th>MRR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGY-1</td>
<td>2.00 (IQR: 21.50)</td>
<td>0.514</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PGY-2</td>
<td>5.00 (IQR: 239.00)</td>
<td>0.355</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PGY-3</td>
<td>2.00 (IQR: 2.75)</td>
<td>0.597</td>
<td>0.003</td>
</tr>
<tr>
<td>PGY-4</td>
<td>2.00 (IQR: 4.00)</td>
<td>0.557</td>
<td>0.003</td>
</tr>
<tr>
<td>Board-certified</td>
<td>1.00 (IQR: 1.00)</td>
<td>0.757</td>
<td>Reference</td>
</tr>
</tbody>
</table>

IQR = interquartile range; PGY = post-graduate year of dermatology residency.

Table 1. Performance of the CDRA with different users. MRR: Mean Reciprocal Rank. P-Value denotes paired Wilcoxon Signed-Rank test, comparing the diagnosis ranks of a dermatology resident to those of a board-certified dermatologist (Reference).

Table 2. Similarity of descriptions of residents compared to the corresponding descriptions of a board-certified dermatologist according to subsections. Results are pooled over all users and cases, lowest values are highlighted in bold.

<table>
<thead>
<tr>
<th>Questionnaire Section</th>
<th>Dice (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrangement</td>
<td>0.75 (95% CI: 0.72-0.79)</td>
</tr>
<tr>
<td>Color</td>
<td>0.75 (95% CI: 0.71-0.79)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>0.96 (95% CI: 0.94-0.97)</td>
</tr>
<tr>
<td>Localization</td>
<td>0.72 (95% CI: 0.69-0.75)</td>
</tr>
<tr>
<td>Morphology</td>
<td>0.57 (95% CI: 0.54-0.60)</td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td>0.85 (95% CI: 0.81-0.89)</td>
</tr>
<tr>
<td>Time</td>
<td>0.62 (95% CI: 0.58-0.65)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Results

Fifty-eight vignettes described by five raters, with one entry of rater PGY-2 missing through a technical error, resulted in 289 probability-ranked diagnosis lists. For all raters, the correct diagnosis was top-1 ranked in most vignettes (Figure 1). While most rankings following inputs of more experienced users fell into the top-8 ranks, inputs by younger participants (PGY-1 & PGY-2) frequently resulted in a very low ranking of the correct diagnosis (> 128; Figure 1). The mean reciprocal rank of the algorithm was 0.757 when applied by the board-certified dermatologist, and significantly lower when applied by residents (Table 1). The highest MRR was measured for benign (0.68; 95% CI: 0.35-1.01) and inflammatory (0.68, 95% CI: 0.46-0.90), the lowest for autoimmune (0.39; 95% CI: 0.02-0.76) and exogenous (0.43; 95% CI: 0.30-0.56) diseases.

Similarity of data entry

The vignettes’ descriptions of the four residents were compared with those of the board-certified dermatologist for similarity. The median Dice-score ranged from 0.64 (95% CI: 0.60-0.67; PGY-2) to 0.74 (95% CI: 0.71-0.77; PGY-3; Suppl. Figure 1). Furthermore, we analyzed the similarities
between the pooled ratings of the residents and the board-certified dermatologist for different subsections of the questionnaire. Inputs for the sections “epidemiology” and “signs & symptoms” obtained the highest average similarity between residents and the board-certified dermatologist (Dice 0.96, [95% CI: 0.94-0.97] and 0.85 [95% CI: 0.81-0.89], respectively). We observed the lowest Dice scores for descriptions of morphology, arrangement and time (Table 2).

**Similarity of inputs regarding morphology and time**

Descriptions for primary lesions (“elevation”, “plane”, “even”) and surface changes (“crust”, “erosion”) were used consistently, whereas descriptions of consistency (“firm”, “soft”, “indurated”) were more ambiguous (Supplementary Figure 2A). Regarding the section of time and disease course (Suppl. Figure 2 B), the terms “recurrent” and “progressive” were used consistently, while the similarity of inputs for the terms “limited”, “self-limited”, and “transient” was rather low.

**Influence of users input on performance of the algorithm**

Complete omission of subsections of the questionnaire deteriorated ranking results. The decrease in performance was most pronounced for the subsections on anatomic site and morphology (Figure 3; Supplementary Table 3). In a small
primary care and in the setting of store-and-forward tele-dermatology [18,25]. We further demonstrate that human understandable symbolic AI fed by human inputs could be a worthwhile alternative to deep learning algorithms for image based diagnostic dermatology. In contrast to deep learning, the rules of symbolic AI are derived from expert knowledge, which facilitates explainability. Aside from that, the rules can be easily adjusted, if errors occur. The disadvantage of this approach, however, is the reproducibility of human inputs. To better pin down potential sources of noise and bias introduced by user inputs, we studied the impact of user expertise on ranking and the similarity of user inputs for corresponding cases. Finally, we also performed a sensitivity analysis to test the robustness of rankings if parts of the clinical description are either missing or misleading. In this respect, we found that the algorithm is most vulnerable to omissions of sections regarding morphology and localization.

**Conclusions**

In this pilot study we conducted an experimental validation of a simple diagnosis ranking algorithm based on comprehensive and structured clinical descriptions provided by physicians. If applied by an experienced user, the algorithm top-ranked the correct diagnosis in the majority of cases. The median rank of the correct diagnosis was not below the fifth position even for the least experienced participant (Figure 1). This means that in a typical use case the correct diagnosis will be included in the first eight ranked diagnoses. The measured accuracy of our approach outperformed similar algorithms in general medicine, in which the top-5 results included the correct diagnosis in about 50% of cases [24].

The subgroup of vignettes, omission of inputs on morphology and color from novices improved the rankings.

**Figure 3.** Rank changes after omission of specific subsections of the questionnaire. Participants were grouped according to experience into novices (left panel; PGY-1 and PGY-2) and experienced users (right panel; PGY-3, PGY-4 and board-certified dermatologist). Dots denote change of rank of the correct diagnosis for one query of one user, boxplots denote median and IQR. The green area highlights changes to a better position, the red area to a worse position. IQR = interquartile range; PGY = post-graduate year of dermatology residency.
even excluded (Figure 1). As the CDRA is structured in sections simulating a bottom-up dermatologic work-up starting with descriptions of primary lesions, we were able to decipher the reasons for these errors in most cases. Considering the inputs of the board-certified dermatologist as the reference standard, the residents’ descriptions were most similar to the reference standard for questions regarding epidemiology, age group, skin type, and additional symptoms (Figure 2). Not unexpectedly, the most ambiguous parts of the questionnaire were the subsections covering morphology and timing.

Haptic elements such as induration were used inconsistently, which can be easily explained by the virtual setting which makes palpation impossible (Supplementary Figure 2A). Follow-up studies with live patients will be necessary to determine whether such elements should be entirely removed from the algorithm or omitted only in image-based case presentations. Analysis of user inputs referring to timing demonstrated that terms describing the course of the disease (“recurrent”, “progressive”, “chronic”; Supplementary Figure 2B) were used rather consistently, but not terms related to resolution (“transient duration”, “self-limited”, “limited”). The explanation may be that experienced users will already know the correct diagnosis and may fabricate a description that is in line with the correct diagnosis, even if the information given in the vignette or by the patient is ambiguous. This points to a limitation of our study since we did not compare diagnostic rankings of users with and without support by the algorithm. The aims of this pilot study, however, were to investigate whether the algorithm is principally feasible for clinical use and to improve the logic of the algorithm and the composition of the questionnaire upon the results of this small-scale experiment, if necessary. Our results show that the performance of the algorithm will depend on the quality of user inputs. To improve the evolution of this and similar algorithms, developers need to focus not only on machine learning issues but also on the user interface and how to minimize noise and bias. The results of our study indicate that it is crucial to select variables that are equally robust and relevant. The number of variables and the time spent for data input will significantly impact the user friendliness of the interface. Poor user friendliness and time spent for data input will significantly impact the user interface and how to minimize noise and bias. The results of this and similar algorithms, developers need to focus not only on machine learning issues but also on the user interface and how to minimize noise and bias.

In conclusion, we demonstrated that our previously described clinical diagnosis ranking algorithm performed well across a wide range of dermatologic. In our small rater group, we found inconsistent input from inexperienced users, who are an important target population of this algorithm, introduced noise and bias and decreased its performance.

Acknowledgements

We want to thank the residents that participated in this study, Arno Lukas from emergentec biodevelopment GmbH for the help in creating the initial graphical user interface of the algorithm, and Gernot Salzer as well as Rodriguez Dominguez Rosa María for the algorithm testing tool.

Ethics approval

The study was reviewed and approved by the Institutional Review Board of the Medical University of Vienna, Austria (protocol-no: 1758/2013), and conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Patient consent

Not required.

References

10.1038/s41591-020-0942-0. PMID: 32372267.


Application of an Interactive Diagnosis Ranking Algorithm in a Simulated Vignette-based Environment for General Dermatology

Antonia Wesinger, Elisabeth Riedl, Harald Kittler, Philipp Tschandl
Supplementary Table 1. Rater characteristics. Information about the five raters with their respective academic title, gender and level of training.

<table>
<thead>
<tr>
<th>Rater</th>
<th>Title</th>
<th>Gender</th>
<th>Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MD</td>
<td>male</td>
<td>PGY-1</td>
</tr>
<tr>
<td>2</td>
<td>MD</td>
<td>female</td>
<td>PGY-2</td>
</tr>
<tr>
<td>3</td>
<td>MD</td>
<td>male</td>
<td>PGY-3</td>
</tr>
<tr>
<td>4</td>
<td>MD</td>
<td>female</td>
<td>PGY-4</td>
</tr>
<tr>
<td>5</td>
<td>MD</td>
<td>female</td>
<td>board-certified</td>
</tr>
</tbody>
</table>

MD = medical doctor; PGY = post-graduate year of dermatology residency.

Supplementary Table 2. Included Patient Vignettes. Alphabetic list of diagnosis vignettes with their allocated disease category, and demographic data. The skin-type is provided on the Fitzpatrick-Scale, as assessed by author PT on digital images.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Category</th>
<th>Age</th>
<th>Age group</th>
<th>Sex</th>
<th>Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne vulgaris</td>
<td>Inflammatory</td>
<td>17</td>
<td>adolescent</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>Inflammatory</td>
<td>57</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Amyloidosis, primary systemic</td>
<td>Other</td>
<td>47</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Angiosarcoma, cutaneous of the elderly</td>
<td>Malignant</td>
<td>78</td>
<td>elder</td>
<td>male</td>
<td>III-IV</td>
</tr>
<tr>
<td>Arthropod Assault, general</td>
<td>Exogenous</td>
<td>23</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Ashy dermatosis</td>
<td>Exogenous</td>
<td>34</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Basal cell carcinoma, general</td>
<td>Malignant</td>
<td>53</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Basal cell carcinoma, pigmented</td>
<td>Malignant</td>
<td>61</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Basal cell carcinoma, ulcerated</td>
<td>Malignant</td>
<td>47</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Borreliosis, general</td>
<td>Infections</td>
<td>27</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Bullous pemphigoid, vesiculo-bullous stage</td>
<td>Autoimmune</td>
<td>68</td>
<td>elder</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Candidiasis, mucocutaneous</td>
<td>Infections</td>
<td>43</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Darier disease</td>
<td>Hereditary</td>
<td>63</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Deep fungal Infection</td>
<td>Infections</td>
<td>34</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Autoimmune</td>
<td>24</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Dermatofibroma</td>
<td>Benign</td>
<td>30</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>Malignant</td>
<td>28</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Autoimmune</td>
<td>47</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Dermatophytosis, general</td>
<td>Infections</td>
<td>53</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Drug eruption, general</td>
<td>Allergic</td>
<td>67</td>
<td>elder</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Dyshidrotic dermatitis</td>
<td>Inflammatory</td>
<td>24</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Epidermal nevus</td>
<td>Benign</td>
<td>17</td>
<td>adolescent</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Epidermolysis bullosa junctional, lethal subtype (letalis)</td>
<td>Hereditary</td>
<td>1</td>
<td>infant</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Erysipelas</td>
<td>Infections</td>
<td>53</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Erythema annulare centrifugum</td>
<td>Inflammatory</td>
<td>37</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Erythema multiforme, general</td>
<td>Allergic</td>
<td>23</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>Inflammatory</td>
<td>35</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Fibrous papule of the face</td>
<td>Benign</td>
<td>53</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Folliculitis, general</td>
<td>Infections</td>
<td>26</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Graft-versus-host disease, acute</td>
<td>Inflammatory</td>
<td>57</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Granuloma annulare, localized</td>
<td>Inflammatory</td>
<td>34</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Hemorrhage, subungual</td>
<td>Exogenous</td>
<td>32</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
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</tbody>
</table>

Supplementary Table 2 continues
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Category</th>
<th>Age</th>
<th>Age group</th>
<th>Sex</th>
<th>Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus infection, disseminated</td>
<td>Infections</td>
<td>78</td>
<td>elder</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Infections</td>
<td>12</td>
<td>child</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Impetigo contagiosa</td>
<td>Infections</td>
<td>8</td>
<td>child</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Kaposi sarcoma, AIDS-related epidemic type</td>
<td>Malignant</td>
<td>47</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Keloid</td>
<td>Exogenous</td>
<td>21</td>
<td>adolescent</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
<td>Hereditary</td>
<td>15</td>
<td>adolescent</td>
<td>female</td>
<td>III-IV</td>
</tr>
<tr>
<td>Leishmaniasis, cutaneous</td>
<td>Infections</td>
<td>23</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Lentigo simplex</td>
<td>Benign</td>
<td>23</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Lentigo, solar</td>
<td>Benign</td>
<td>72</td>
<td>elder</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis</td>
<td>Inflammatory</td>
<td>39</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Lichen planus, general</td>
<td>Inflammatory</td>
<td>37</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Lichen planus, oris</td>
<td>Inflammatory</td>
<td>37</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Lupus erythematosus, subacute cutaneous</td>
<td>Autoimmune</td>
<td>23</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Lymphoma, general</td>
<td>Malignant</td>
<td>66</td>
<td>elder</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Mammary Paget’s disease</td>
<td>Malignant</td>
<td>53</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Melanoma in situ, general</td>
<td>Malignant</td>
<td>57</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Melanoma in situ, lentigo maligna</td>
<td>Malignant</td>
<td>72</td>
<td>elder</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Melanoma, acral lentiginous type</td>
<td>Malignant</td>
<td>34</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Melanoma, lentigo maligna type</td>
<td>Malignant</td>
<td>82</td>
<td>elder</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Melanoma, superficial spreading type</td>
<td>Malignant</td>
<td>34</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Melasma</td>
<td>Other</td>
<td>50</td>
<td>adult</td>
<td>female</td>
<td>V-VI</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Infections</td>
<td>5</td>
<td>infant</td>
<td>male</td>
<td>I-II</td>
</tr>
<tr>
<td>Mycosis fungoides, plaque stage</td>
<td>Malignant</td>
<td>45</td>
<td>adult</td>
<td>female</td>
<td>III-IV</td>
</tr>
<tr>
<td>Mycosis fungoides, patch stage</td>
<td>Malignant</td>
<td>66</td>
<td>elder</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Necrobiosis lipoidica</td>
<td>Inflammatory</td>
<td>55</td>
<td>adult</td>
<td>female</td>
<td>I-II</td>
</tr>
<tr>
<td>Nummular dermatitis</td>
<td>Inflammatory</td>
<td>62</td>
<td>adult</td>
<td>male</td>
<td>I-II</td>
</tr>
</tbody>
</table>

**Supplementary Table 3.** Rank changes after omission of subsections of the questionnaire. Results of all users are pooled. P values refer to the Wilcoxon signed rank test.

<table>
<thead>
<tr>
<th>Section omitted</th>
<th>Rank change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Median: 0.00 (IQR: 1.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arrangement</td>
<td>Median: 0.00 (IQR: 1.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Localization</td>
<td>Median: -1.00 (IQR: 4.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Morphology</td>
<td>Median: -1.00 (IQR: 3.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Color</td>
<td>Median: 0.00 (IQR: 1.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time</td>
<td>Median: 0.00 (IQR: 1.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td>Median: 0.00 (IQR: 0.00)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

IQR = interquartile range.
Supplementary Figure 1. Similarity of full case descriptions between residents and the board-certified dermatologist, measured with the Sørensen-Dice index. Boxplots denote median and IQR, dots denote the value of a single case description comparison.

IQR = interquartile range; PGY = post-graduate year of dermatology residency.

Supplementary Figure 2. Term frequency per case as a surrogate for robustness. Minimum is 1, as only terms used at least once were included, maximum is 5 as five raters participated. In case a term is used only within one case, no distribution measurement such as standard deviation (SD) can be calculated.
An Updated Algorithm Integrated With Patient Data for the Differentiation of Atypical Nevi From Early Melanomas: the idScore 2021

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Key words: melanoma, atypical nevi, dermoscopy, risk factors


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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: It is well known that multiple patient-related risk factors contribute to the development of cutaneous melanoma, including demographic, phenotypic and anamnestic factors.

Objectives: We aimed to investigate which MM risk factors were relevant to be incorporated in a risk scoring-classifier based clinico-dermoscopic algorithm.

Methods: This retrospective study was performed on a monocentric dataset of 374 atypical melanocytic skin lesions sharing equivocal dermoscopic features, excised in the suspicion of malignancy. Dermoscopic standardized images of 258 atypical nevi (aN) and 116 early melanomas (eMM) were collected along with objective lesional data (i.e., maximum diameter, specific body site and body area) and 7 dermoscopic data. All cases were combined with a series of 10 MM risk factors, including demographic (2), phenotypic (5) and anamnestic (3) ones.

Results: The proposed iDScore 2021 algorithm is composed by 9 variables (age, skin phototype I/II, personal/familiar history of MM, maximum diameter, location on the lower extremities (thighs/legs/ankles/back of the feet) and 4 dermoscopic features (irregular dots and globules, irregular streaks, blue gray peppering, blue white veil). The algorithm assigned to each lesion a score from 0 to 18, reached an area under the ROC curve of 92% and, with a score threshold ≥ 6, a sensitivity (SE) of 98.2% and a specificity (SP) of 50.4%, surpassing the experts in SE (+13%) and SP (+9%).
Conclusions: An integrated checklist combining multiple anamnestic data with selected relevant dermoscopic features can be useful in the differential diagnosis and management of eMM and aN exhibiting with equivocal features.

Introduction
An adequate dermoscopic differentiation between atypical melanocytic skin lesions (aMSLs), ie, atypical nevi (aN) and early melanomas (eMM) can represent a challenge in daily practice, especially for less experienced dermatoscopists. Dermoscopy alone cannot be accurate enough to adequately recognize aN exhibiting equivocal dermoscopic feature or, of converse, can fail to identify those eMM that do not exhibit clear-cut dermoscopic features suggestive for malignancy [1-6]. In addition, we also debate whether a certain degree of overdiagnosis of in situ MM might have took place in the last decade worldwide [7-10]. In this context, a reasonable way out seems to be to follow a global approach to the patient integrating dermoscopic imaging with multiple risk assessment tools and personal plus lesional data [7,11-18].

Objectives
We previously demonstrated the efficacy of integrating 3 relevant clinical parameters (ie, age, maximum diameter and body location) into a dermoscopic algorithm (the iDScore 2018) [1], which reached high diagnostic accuracy on both a monocentric dataset of 435 aMSLs and on a multicentric dataset of 980 aMSLs. We then aimed to extend the list of clinical parameters to the most relevant potential melanoma risk factors and to investigate which were the most significant independent association with a MM histologic diagnosis. Secondly, we aimed to select through stepwise logistic regression analysis a series of interdependently significant data, useful to develop a new iDScore 2021 checklist, able to provide a differential score to distinguish eMM from aN with equivocal features.

Methods
This retrospective study was realized in accordance with the Declaration of Helsinki and approved by the local ethical committee (ID16801); all data were de-identified before use.

Data Collection
A total of 410 aMSLs were consecutively excised from January 2018 to May 2021 in Siena University Hospital in the suspicion of malignancy. All aMSLs localized on the face, palms, and soles were excluded a priori due to their specific dermoscopic pattern. Histological diagnoses were retrospectively collected, including dermoscopic standardized polarized images (OM 20X) have been prospectively collected along with lesional data (maximum diameter and body location based on a sun-exposure classification), as previously described [14]. In addition, patients personal data concerning 8 MM risk factors were collected, ie: personal/familiar history of MM; sunburns before 14 years, phototype, pheomelanin, blond hairs, blue/green eyes, >11 nevi on the right arm (Table 1). The presence of pheomelanin phenotype was assessed when the patient had red/carrot/y/straw red/brown-reddish hair, pale skin, freckles and high tendency to sunburn and/or inability to tan.

Dermoscopic-reader Study
Dermoscopic evaluations were independently performed by 4 experts in dermoscopy, blinded for histopathological diagnosis (EC, MB, AL, PR). They were asked to recognize a dermoscopic feature among a series of 7, previously selected for the iDScore 2018 checklist (Tables 1 and 4), including: Atypical Network (AN), Irregular Streaks (IS), Blue White Veil (BWV), Blue Gray Peppering (BGP), White Scar-like Areas (WSA), Shiny White Streaks (SWS) and Irregular Dots Globules (IDG) (Figures 1 and 2). Then, they were asked to express an intuitive diagnosis of eMM/aN. The presence of one or more dermoscopic features inside each lesion and the final diagnosis was assessed based on the agreement of 3 out of 4.

Integrated dataset
After selection (MG, LT, AC) for image quality, availability of patient data and agreement of 2 out of 3 pathologists on histopathological diagnosis, the final database consisted of 374 standardized dermoscopic pictures, 258 and 116 eMM. Each lesion was paired with 19 objective parameters, including: 8 MM risk factors, 2 patient demographic data, 2 aMSL objective data and 7 dermoscopic features (Table 1).

Statistical analysis
Descriptive analysis was carried out using absolute frequencies and percentages for qualitative variables, mean and standard deviation for age and diameter, median and minimum-maximum range for the iDScore. Age and diameter were then categorized for the score model purpose, merging classes with same risk. The association of gender, risk
factor and clinical features with histology were evaluated by chi-squared test. The difference of age and diameter between aN and eMM by t test, instead, the iDScore by Mann-Whitney test. Kolmogorov-Smirnov test was used to evaluate the normality distribution of quantitative variables. Bivariate analysis was performed by logistic regression, the Odds Ratios (OR) and their 95% confidence interval (CI) were estimated, too. In particular, eight bivariate logistic regression were carried out, each one with iDScore plus one risk factor. After that, an integer score model was developed based on logistic regression. Leave-one-out procedure was used for testing the model. ROC curves and their areas (AUROC) were also estimated to compare the model performances. A P < 0.05 was considered statistically significant. The analyses were carried out with R version 4.10.

Results

Case study

In Table 1 is reported the distribution of all patient demographic data (2), the melanoma risk factors (8) and the aMSLs morphologic data (2). Concerning the eMM, they affected males in 53% versus females in 46% of cases, mean age was 58.9 years, the predominant body area was the upper trunk (49% of cases) and the average diameter was 9.5mm. Histologic stages included: Tis (50), Ia (37), Ib (20) and Ila (9 cases) [19].

Table 1. Distribution of patient demographic data, melanoma risk factors and lesional data in the case study iDScore database 2018-2020 of 374 atypical melanocytic skin lesions. The results of univariate analysis for significant association with MM histologic diagnosis are also reported with corresponding P-values.

<table>
<thead>
<tr>
<th></th>
<th>Atypical nevi (aN) N=258</th>
<th>Early melanomas (eMM) N=116</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Age (years)</td>
<td>48.0±14.2</td>
<td>58.9±15.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2. Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>106 (41.1%)</td>
<td>54 (46.6%)</td>
<td>0.366</td>
</tr>
<tr>
<td>Male</td>
<td>152 (58.9%)</td>
<td>62 (53.4%)</td>
<td></td>
</tr>
<tr>
<td>Anamnestic risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. History of melanoma (personal / 1° relative)</td>
<td>72 (28.2%)</td>
<td>50 (43.1%)</td>
<td>0.007</td>
</tr>
<tr>
<td>2. Sunburns before 14 (yes/no)</td>
<td>173 (68.7%)</td>
<td>82 (71.9%)</td>
<td>0.542</td>
</tr>
<tr>
<td>3. Smoke (&gt;5 cigarettes/day) (yes/no)</td>
<td>66 (26.3%)</td>
<td>19 (22.1%)</td>
<td>0.475</td>
</tr>
<tr>
<td>Phenotypic risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Skin phototype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I+II</td>
<td>66 (25.8%)</td>
<td>60 (51.7%)</td>
<td>0.005</td>
</tr>
<tr>
<td>III+IV</td>
<td>190 (74.2%)</td>
<td>56 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>5. Pheomelanin phenotype (yes/no)</td>
<td>23 (9.0%)</td>
<td>21 (18%)</td>
<td>0.005</td>
</tr>
<tr>
<td>6. Blonde hair (yes/no)</td>
<td>42 (16.4%)</td>
<td>28 (24.3%)</td>
<td>0.05</td>
</tr>
<tr>
<td>7. Green/light-blue/blue eyes (yes/no)</td>
<td>86 (33.7%)</td>
<td>43 (37.4%)</td>
<td>0.556</td>
</tr>
<tr>
<td>8. &gt;11 nevi/right arm (yes/no)</td>
<td>128 (50.4%)</td>
<td>66 (57.4%)</td>
<td>0.005</td>
</tr>
<tr>
<td>aMSLs data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Maximum diameter (mm)</td>
<td>6.4±2.5</td>
<td>9.5±3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. Body area / anatomical site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Extremities - chronically photoexposed [head/neck/arms/hands]</td>
<td>18 (7.0%)</td>
<td>14 (12.1%)</td>
<td>0.113</td>
</tr>
<tr>
<td>Upper Trunk - seldom photoexposed [shoulders/back/chest/breast]</td>
<td>146 (56.6%)</td>
<td>57 (49.1%)</td>
<td>0.217</td>
</tr>
<tr>
<td>Lower Extremities - frequently photoexposed [thighs/legs/ankles/back of the feet]</td>
<td>26 (10.1%)</td>
<td>18 (15.5%)</td>
<td>0.164</td>
</tr>
<tr>
<td>Lower Trunk - rarely photoexposed [side/bottom/abdomen]</td>
<td>68 (26.4%)</td>
<td>27 (23.3%)</td>
<td>0.608</td>
</tr>
</tbody>
</table>

Table 1 continues
Table 1. Distribution of patient demographic data, melanoma risk factors and lesional data in the case study iDScore database 2018-2020 of 374 atypical melanocytic skin lesions. The results of univariate analysis for significant association with MM histologic diagnosis are also reported with corresponding P-values. (Continued)

<table>
<thead>
<tr>
<th>8 variables/melanoma risk factors</th>
<th>Atypical nevi (aN) N=258</th>
<th>Early melanomas (eMM) N=116</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ranges 31-60 years</td>
<td>104 (89.7%)</td>
<td>104 (89.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>&gt;11 nevi/right arm</td>
<td>230 (89.1%)</td>
<td>29 (11.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of MM (personal/1st relative)</td>
<td>21 (8.1%)</td>
<td>28 (24.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sunburns</td>
<td>29 (11.2%)</td>
<td>49 (39.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin phototype (I+II vs III+IV)</td>
<td>18 (7.0%)</td>
<td>29 (25.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pheomelanin phenotype</td>
<td>21 (8.1%)</td>
<td>28 (24.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Green/light-blue/blue eyes</td>
<td>1 (0.4%)</td>
<td>4 (3.4%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Smoke (&gt;5 cigarettes/day)</td>
<td>71 (27.5%)</td>
<td>60 (51.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>iDScore 2018</td>
<td>6 [2-11]</td>
<td>9 [4-14]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Dermoscopic-reader study
The presence of 7 dermoscopic variables in the 2 groups of aN and eMM according to experts consensus (ie, number of positive observation, %) is also reported in Table 1. The 4 experts in dermoscopy obtained, on average, a sensitivity (SE) and specificity (SP) of 85.2% and 41.5%, respectively, on the present dataset of difficult aMSLs.

Univariate analysis
A total of 12 variables resulted more frequently associated with a eMM diagnosis rather than with aN diagnosis, and to significantly discriminate (P < 0.05) the 2entities, namely: “age”, “history of MM (personal / 1st relative)”, “skin phototype I/II”, “pheomelanin phenotype”, “>11 nevi/right arm”, “maximum diameter” and the presence of IS, BWV, BGP, WSA, SWS and IDG (Table 1).

Table 2. Bivariate analysis of the 8 variables/melanoma risk factors combined with the iDScore 2018 checklist and association with MM histologic diagnosis.

<table>
<thead>
<tr>
<th>8 variables/melanoma risk factors</th>
<th>iDScore 2018 checklist + new variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;11 nevi/right arm</td>
<td>OR (95% CI) 1.1 (0.6-2.3)</td>
</tr>
<tr>
<td>History of MM (personal/1st relative)</td>
<td>2.8 (1.4-5.4)</td>
</tr>
<tr>
<td>Sunburns</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td>Skin phototype (I+II vs III+IV)</td>
<td>2.9 (1.5-5.6)</td>
</tr>
<tr>
<td>Pheomelanin phenotype</td>
<td>1.5 (0.7-3.6)</td>
</tr>
<tr>
<td>Green/light-blue/blue eyes</td>
<td>1.0 (0.6-2.0)</td>
</tr>
<tr>
<td>Blonde hair</td>
<td>1.3 (0.6-2.7)</td>
</tr>
<tr>
<td>Smoke (&gt;5 cigarettes/day)</td>
<td>1.1 (0.5-2.4)</td>
</tr>
</tbody>
</table>

CI = Confidence Interval; OR Odds ratio.

Bivariate analysis
Each one of the 8 variables assumed as possible MM risk factors was tested in combination with the iDScore 2018 checklist for the association with MM histologic diagnosis: according to the bivariate analysis results (Table 2), it appeared that only 2 variables added a significant increase in accuracy when incorporated into the previous checklist iDScore 2018, namely the “skin phototype I/II” and the “history of MM” (personal or regarding the 1st degree relative).

Logistic regression
According to the stepwise analysis of the logistic regression (Table 3), the new iDScore 2021 checklist would be composed by only 9 parameters, including the "age ranges 31-60 years" and ≥ 61 years, the “skin phototype I/II”, the “history of MM”, the “maximum diameter” ranges 6-10mm.
and ≥11mm, the “body location on the lower Extremities (including thighs/legs/ankles/back of the feet), and presence of 4 dermoscopic variables such as IDG, IS, BWV and BGP.

**Performance analysis of the integrated model**

Table 4 illustrates the composition of the iDScore 2018 and the new iDScore 2021 model, the partial scores (coefficients) assigned to each variable and the total score (S range) which could be assigned to a given aMSL (from S = 0 to S = 18). In addition, the preferred score threshold (St) for both model is reported, along with the corresponding SE and SP values, while the global performance is expressed as area under the ROC curve with 95% confidence interval. In detail, the iDScore 2021 showed: with St ≥ 6, SE = 98.2%, SP = 50.4 (+0.6% SE and +2.3% SP compared with 2018 model); with St ≥ 5, SE = 100%, SP = 30%; with St ≥ 7, SE = 96.4% and SP=31.7.

In Figures 1 and 2 are reported 6 exemplificative cases, namely 3 aMSL of the back (Figure 1) and 3 aMSLs of the body frequently photo-exposed [thighs / legs / ankles / back of the feet].

**Table 3. Results of the stepwise multivariate logistic regression analysis performed over all variables (2 patient anagraphic data + 8 melanomas risk factors + 2 lesion data + 7 dermoscopic data) for the association with a histologic diagnosis.**

<table>
<thead>
<tr>
<th>9 selected variables (iDScore 2021)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 31-60 years</td>
<td>16.9 (3.0-54.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age ≥ 61 years</td>
<td>89.5 (14.4-889.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximum Diameter 6-10mm</td>
<td>7.4 (3.1-20.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximum Diameter ≥11mm</td>
<td>36.7 (12.1-126.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lower Extremities</td>
<td>3.1 (1.1-8.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>IDG</td>
<td>2.6 (1.4-5.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>IS</td>
<td>5.1 (2.4-11.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BWV</td>
<td>6.7 (2.5-19.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BGP</td>
<td>3.7 (1.5-9.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Phototype (I+II vs III+IV)</td>
<td>3.2 (1.7-6.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of melanoma (personal /1st relative)</td>
<td>3.2 (1.6-6.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

BGP = Blue Gray Peppering; BWV = Blue White Veil; CI = Confidence Interval; IDG = Irregular Dots Globules; IS = Irregular Streaks; OR = Odds ratio.

**Table 4. Comparison of the two models of 2 models of integrated iDScore checklist: composition and performances obtained over 324 atypical melanocytic skin lesions of the body.**

<table>
<thead>
<tr>
<th>composition (iDScore 2018)</th>
<th>coefficient</th>
<th>composition (iDScore 2021)</th>
<th>coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Atypical Network</td>
<td>1</td>
<td>1. Blue white veil</td>
<td>2</td>
</tr>
<tr>
<td>2. Irregular Streaks</td>
<td>1</td>
<td>2. Irregular Streaks</td>
<td>2</td>
</tr>
<tr>
<td>3. Blue White Veil</td>
<td>1</td>
<td>3. Irregular dots and globules</td>
<td>1</td>
</tr>
<tr>
<td>4. Blue Gray Peppering</td>
<td>1</td>
<td>4. Blue Gray Peppering</td>
<td>1</td>
</tr>
<tr>
<td>5. White Scar-like Areas</td>
<td>1</td>
<td>5. Maximum Diameter</td>
<td>2</td>
</tr>
<tr>
<td>6. Shiny White Streaks</td>
<td>1</td>
<td>6-10 mm</td>
<td>2</td>
</tr>
<tr>
<td>7. Irregular Dots Globules</td>
<td>1</td>
<td>≥11 mm</td>
<td>4</td>
</tr>
<tr>
<td>8. Maximum diameter</td>
<td>1</td>
<td>6. Age</td>
<td>3</td>
</tr>
<tr>
<td>9. Age</td>
<td>3</td>
<td>31-60 years</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>≥61 years</td>
<td>5</td>
</tr>
</tbody>
</table>

7. Lower Extremities frequently photo-exposed [thighs / legs / ankles / back of the feet]

**Table 4 continues**
Table 4. Comparison of the two models of integrated iDScore checklist: composition and performances obtained over 324 atypical melanocytic skin lesions of the body. (Continued)

<table>
<thead>
<tr>
<th>composition</th>
<th>coefficient</th>
<th>iDScore 2018</th>
<th>iDScore 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremities -</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chronically photo-exposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremities -</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>frequently photo-exposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper trunk - seldom</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>photo-exposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROC area (CI 95%)</td>
<td>0.904 (0.872-0.935)</td>
<td>0.917 (0.887-0.944)</td>
<td></td>
</tr>
<tr>
<td>Score Range</td>
<td>0-16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score threshold</td>
<td>St ≥ 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(SE = 97.4%; SP = 48.1%)</td>
<td>(SE = 98.2%; SP = 50.4%)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; SE = sensitivity; SP = specificity; st = core threshold

Figure 1. Examples of atypical melanocytic skin lesions (aMSLs) on the upper back from the case study. A 71 years-old male, phototype II, personal history of melanoma, with a 11 mm aMSL, iDScore 2021 = 15 (iDScore 2018 = 9); histological examination revealed an early melanoma (MM T1aN0M0, thickness 0.7mm) (aA and B). A 61 years-old male, phototype II, with 7mm aMSL: the iDScore 2021 was 9 (iDScore 2018 = 7) and the histological examination revealed a nevus with moderate atypia (C and D). A 50 years-old male, 11 mm, phototype II, > 11 nevi/right arm, 1st relative history of MM, sunburns before the age of 14, with a 10mm aMSL: the iDScore 2021 was 10 (iDScore 2018 = 8) and the histological examination revealed a nevus with severe atypia (E and F).
When taking into account the patient demographic data, age confirmed to be a significant independent risk factors for discriminating aN from eMM, with a flexing point of the S-shaped curve for malignancy incidence at 50 years [23-25]. The statistical analyses here conducted on a large data-set of aMSLs were restricted to two crucial cut-offs at 31 and 60 years and allowed to identify three range groups with increasing risk for malignancy (Table 4). Concerning sex, we here observed that sex variable is not a variable to be considered for an algorithm, because aN and eMM are similarly distributed among males and females, in line with recent studies confirming no significancy, but only in association with the UV-exposure habits and/or hormonal changes (ie female sex) [26-28]. Among the patient anamnestic data, the positive history for MM-personal or in a 1st degree relative is still a considered a nonmodifiable risk for the incidence of a new MM [20-23,27,28]. Here in this dataset, this variable

Conclusions

The debate about the relative impact of modifiable and non-modifiable risk factors on melanoma development is still ongoing [20-22]. However, some demographic data related to the patient and some characteristics of the lesion itself have currently acquired a considerable body of evidence and deserve to be investigated as possible additional risk score coefficients along with the dermoscopic parameters [1,2,11,13,14].

When taking into account the patient demographic data, age confirmed to be a significant independent risk factors for discriminating aN from eMM, with a flexing point of the S-shaped curve for malignancy incidence at 50 years [23-25]. The statistical analyses here conducted on a large data-set of aMSLs were restricted to two crucial cut-offs at 31 and 60 years and allowed to identify three range groups with increasing risk for malignancy (Table 4). Concerning sex, we here observed that sex variable is not a variable to be considered for an algorithm, because aN and eMM are similarly distributed among males and females, in line with recent studies confirming no significancy, but only in association with the UV-exposure habits and/or hormonal changes (ie female sex) [26-28]. Among the patient anamnestic data, the positive history for MM-personal or in a 1st degree relative is still a considered a nonmodifiable risk for the incidence of a new MM [20-23,27,28]. Here in this dataset, this variable

Figure 2. Examples of atypical melanocytic skin lesions (aMSLs) of the chest from the case study. A 80 years-old male, phototype III, familiar history of melanoma, with a 7 mm aMSL; iDScore 2021 was 12 (iDScore 2018 = 8) and the histological analysis revealed an in situ melanoma (A and B). A 66 years-old male, phototype II, familiar history of MM, with a 10 mm aMSL: the iDScore 2021 was 10 (iDScore 2018 = 8); the histological analysis revealed a nevus with moderate atypia (C and D). A 47 years-old female, phototype III, with a 7.7 mm aMSL, the iDScore 2021 was 6 (iDScore 2018 = 5) and the histological examination revealed a compound nevus (E and F).
Many studies have been carried out in squamous cell carcinoma of the skin, psoriasis and impaired cigarette smoke was correlated with premature skin aging, renowned as a risk factor for several types of human cancer, in discriminating among the two entities (Tables 2 and 3). Nevi (69%) and eMM (70%), which resulted not significant of patient with dysplastic nevus syndrome/multiple atypical nevus (69%) and melanoma among relatives with the same phenotype, but results were not univocal or clear-cut due to residual statistical confounders or inadequate sample size [36-38]. In a recent case-control study carried out over 1,157 patients diagnosed with MM and 5,595 controls in the Netherlands, cigarette smoking was found not to increase the risk of MM development, as well as in a large cohort study on US white women [39,40]. Similarly, here in this study we find the smoke habit to involve 26% of patients from the aN group and 21% of patients from the eMM group (Table 1) and not to impact significantly on the differential diagnosis among these two entities (Tables 2 and 3).

In the last decade, the parameter “total nevi number” was investigated in adult European and American population as possible MM risk factor, both independently or in association with other parameters (MM body site distribution, patient height, etc.) [37,39-43]: the high nevus count > 50 of the whole body appeared to be independently associated with MM incidence, and high nevus count on the extremities (ie photo-exposed areas) appeared to bring more risk than high nevus count on the trunk [37,40,42,44]. Then, several investigations were carried out to find a valid esteem of the total body count taking into account the nevi count on the 4 extremities, on the upper extremities (> 20), on the lower extremities (> 10) or on the right arm (> 11) [37,40,42,44]. To facilitate the risk factors collection in clinical practice, we decided to adopt the cut-off of > 11 nevi on the right arm as predictor of the total nevi count, based on current literature knowledge. When investigating this parameter in our adult population of patients with aMSLs, similar rates of high nevus count in both the eM (53%) and the aN (50%) group (Table 1), and it was not selected by multiple regression analysis. Indeed, our aN group population hosts a considerable quote of patients with multiple Clark nevus phenotype, as occur in many second level referring ambulatories for screening and follow-up. There are however data suggesting that the MM incidence is higher in patients with multiple aN/Clark nevi in addition to a family history of melanoma among relatives with the same phenotype, but low among people with sporadic phenotype of multiple Clark nevi [45,46]. Consequently, the nevus count is not a discriminant variable for distinguishing aN form EMs, but should be evaluated along with the nevi characteristics, such as the stability/change during follow-up and additional patient data (eg the “Clark phenotype”).

Finally, we took into account the impact of all physical characteristics related to melanin type, including the skin phototype of the patient, its hair color, the eye color and the presence/absence of a pheomelanin phenotype. The presence of blond hair and of blue/light-blue or green color were traditionally investigated as risk factor for skin cancer [46-48]. First studies in northern Europe population-based studies, the light eye color emerged as independently associated risk factor for MM development (~1.6-fold higher risk for MM compared with dark eyes), while the blond hair color had moderate risk [45-48]; more recently, Spanish population-based study revealed that hair and eye color did
not show any significant effects even after adjustments for confounders [44].

Here in this study based on a southern European population, the univariate analysis (Table 1) demonstrated that the discriminant independent power of the variables “fair phenotype”, “blonde hair” and “green/light-blue/blue eyes” is similar. Moreover, a significant discrimination is obtained when comparing phenotypes I-II versus phenotypes III+IV, in line with literature data that assigned a 3-fold higher risk when comparing phenotypes I+II versus phenotypes III+IV, is similar. Moreover, a significant discrimination is obtained when comparing phenotypes I-II vs phenotypes III+IV, in line with literature data that assigned a 3-fold higher risk when comparing phenotypes I+II vs phenotypes III+IV.

However, the multivariate logistic regression analysis selected the variable fair skin phenotype (I-II) (Table 4) instead of the two variables “blonde hair” and “light-colored eyes”: these two were likely to be statistically “absorbed” by the fair phototype variable, which is nevertheless considered an including category.

Of converse, the “pheomelanin phototype” is assessed in a patient exhibiting when red/carrotty/reddish hair, pale skin and freckles in combination with the high tendency to sunburn and/or inability to tan [45-50]. Recent molecular studies in vitro and in vivo on mouse models (including inactivated mutation of the MC1R gene and BRAFV600E mutation) suggest that the pheomelanin phototype may facilitate skin carcinogenesis through either an UV-dependent (ie accumulation of DNA damage through oxidative stress) and an UV-independent pathway [49-50]. It is understood that this parameter should be regarded as a body-site and sun-exposure independent risk factor for MM, with reported with rates between 1.4 and 3 [45-48]. We indeed observed a discriminant power for this parameter in the dd between aN and EMs (P = 0.005) according to univariate analysis (Table 1).

When comparing the new iDScore 2021 checklist with its precursor iDScore 2018 (Table 4), some differences can be highlighted.

First, the training phase was based on a total of 19 parameters (3 anamnestic risk factors + 5 phototypic risk factors + 2 anagraphic data + 2 aMSL data + 7 aMSLs dermoscopic features) instead of the 10 parameters (2 anagraphic data + 2 aMSL data + 7 aMSLs dermoscopic features) of the iDScore 2018.

Second, some modifications were applied in order to simplify the checklist final use: estimation of 3 age groups with different coefficient instead of using 4 age groups; selection of one body area with the high discriminant power, instead of using 3 body areas; reduction of dermoscopic variables from 7 to 4. Concerning this final selection of 4 inter-dependently significant dermoscopic variables, the 3 left out were: White Scar-like Areas, Shiny White Streaks and Atypical network. White Scar-like Areas and Shiny White Streaks were significant in the univariate analysis, but not in the multivariate analysis, as they did not reached significant numerosity in the whole dataset. Importantly, the atypical network was similarly observed in both the aN and eMM groups (89.1% and 89.7% of cases, respectively) (Table 1) thus cannot be considered a discriminant factor. Thus, the differential diagnosis of aN and eMM equivocal images, concerning this monocentric dataset, relies essentially on the combination of 4 dermoscopic variables: “Blue white veil”, “Irregular Streaks, Irregular dots and globules” and “Blue Gray Peppering” (Table 4).

Third, for the final checklist composition, the selection based on multivariate analysis was restricted to the most relevant independent 9 integrated variables, to respect the feasibility requirement for using the checklist in daily practice without reducing the accuracy [1,13].

Fourth, the total score range of iDScore 2021 is wider, from 0 to 18, while for iDScore 2018 was 0-16 (Table 4, Figures 1 and 2).

Concerning the performance comparison of the two models, when tested on the same monocentric dataset of 324 aMSL, the new iDScore 2021 appeared to be more accurate (ROC area=92%, SE=98%, SP=50%) then the iDScore 2018 (ROC area = 90%, SE = 97%, SP = 48%) (Table 4, Figure 3), and to surpass the experts in terms of SE (+13%) and SP (+9%).

The present study has some limitations. First, although the number of eMM lesions selected was enough to obtain an adequate discriminant power, the whole sample size was limited. Secondly, the evaluators were forced to use a series of selected dermoscopic parameters (ie iDScore checklist 2018) in the dermoscopic pattern analysis: this selection of 7 dermoscopic criteria has a practical value but could also be regarded as a bias in the sense that some recent additional terminology/dermoscopic features of aN and eMM is preventively excluded.

Taken together, the present findings suggest the following considerations. First, the investigation approach of developing a scoring checklist based on an integrated dataset of patients demographic, phenotypic and anamnestic risk factors integrated with objective clinical and dermoscopic data could help dermatologists in early identification of the patient with high risk of MM in routine medical consultations. Second, using an integrated risk score algorithm such as the new 2021 iDScore checklist with 9 parameters, each one associated with a peculiar partial score, could be proposed as a rapid and easy tool to screen patients with multiple aMSLs and assign them a progressive predictive score ranging from an aN to an eMM diagnosis based on statistical probability. Third, managing these patients according to the peculiar aMSL risk score could help not only in reducing the rate of inappropriate excision for benign lesions but also in organizing the proper follow-up timing (3/6/9/12 months) during daily practice.
Further studies on larger integrated datasets from multiple centers are required to confirm the validity of the present approach and proceed to the testing phase of the proposed integrated checklist.

References


Comparison of Early and Late Onset Psoriasis (EOP and LOP) Regarding Systemic Inflammatory Comorbidities: LOP is a More Rapid Subtype of Psoriasis

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Key words: psoriasis, comorbidity, early onset psoriasis, late onset psoriasis, inflammation

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Introduction: Early onset psoriasis (EOP) and late onset psoriasis (LOP) differ regarding genetic background, clinical presentation and course of disease.

Objectives: In this study, comparison of EOP and LOP regarding systemic inflammatory comorbidities which are frequently seen in psoriasis and determination of possible differences is aimed.

Methods: A total of 160 plaque psoriasis patients (121 with EOP and 39 with LOP) were enrolled for the study. Data was collected with face-to-face questionnaire and patients medical chart evaluation. Collected data included medical and family history, clinical features and parameters indicating severity of psoriasis, results of laboratory work-up, physical and dermatological examination findings, presence of joint and nail involvement and associated inflammatory systemic comorbidities such as cardiovascular diseases (CVD), diabetes mellitus (DM), hypertension (HT), metabolic syndrome (MS), obesity.

Results: Nail involvement and PsA occurred more rapidly in LOP compared to EOP (P < 0.01, P < 0.01). Compared frequencies in LOP and EOP were 7.7% versus 0.8% for CVD, 38.5% versus 14% for HT, 33.3% versus 9.9% for DM and 44.7% versus 24.8% for MS, respectively. CVD, HT, DM and MS were significantly more frequent in LOP compared to EOP (P = 0.045, P = 0.001, P < 0.01, P = 0.022). Results of multivariate analysis performed taking into account the age, gender, severity parameters of disease, alcohol consumption, smoking habits and other concurrent systemic comorbidities revealed LOP to be an independent risk factor for CVD and DM (P < 0.01, R²: 0.036, P < 0.01, R²: 0.077).

Conclusions: LOP seems to interact with systemic comorbidities hence generates more severe inflammatory burden and shows a more rapid course.
Introduction

Psoriasis is a chronic, multifactorial inflammatory skin disease with a polygenic background and variable clinical presentations. Nowadays, it is more frequently referred as “psoriatic disease” due to its association with systemic co-morbidities such as psoriatic arthritis (PsA), obesity (OB), cardiovascular diseases (CVD), diabetes mellitus (DM), hypertension (HT), metabolic syndrome (MS) and inflammatory bowel diseases (IBD).

Psoriasis is classified based upon phenotypic presentation, association with human leukocyte antigen (HLA) and age at onset [1]. Henseler and Christophers have observed that clinical characteristics of psoriasis differ according to the age of onset [2]. In patients who developed psoriasis before age 40, psoriasis tends to be more severe, recurrent and resistant to treatment. Thus, they offered new classification of psoriasis based upon the age of onset; psoriasis which developed before 40 years was accepted as early onset psoriasis (EOP) and psoriasis which developed after 40 years as late onset psoriasis (LOP). Although this cut-off point have been used by several authors, others have used a wide range of cut-off point (30-50 years), thus limiting comparisons between studies [1,3–6].

Differences in the clinical characteristics and course of the disease, response to treatment, genetic predisposition and psychosocial effects in EOP and LOP have been reported in previous studies. EOP have been shown to be more severe and pose recurrent flares, positive family history, Koebner phenomenon and association with HLA-C [3–5,7–9]. EOP was also claimed to have more prominent psychosocial effect and requirement for systemic treatment is usually more frequent [1,7,10]. Epidemiologic studies have demonstrated association of psoriasis with systemic inflammatory diseases, but to our knowledge there is only one report comparing EOP and LOP regarding concomitant systemic inflammatory comorbidities, which found OB to be more frequent in LOP than EOP [1].

Objectives

Based on previous literature and lack of data in this aspect, we aimed to compare inflammatory comorbidities along with clinical characteristics and severity of psoriatic disease and possibly determine differences in EOP and LOP in this study.

Methods

Patients

Data was collected by a face-to-face questionnaire and medical chart evaluation. Patients older than 18 years of age with plaque psoriasis who were on follow-up at our department of dermatology between 1st October 2018 and 1st March 2019 were enrolled for the study. Patients with disease onset before age of 40 years were accepted as EOP and patients with disease onset equal or after 40 years were considered to have LOP. The study was approved by the ethic committee of non-invasive clinical studies of Hacettepe University (ID GO 18/1057-30).

Methods

Questionnaire

The face-to-face questionnaire consisted of 5 main sections: (1) patient demographics; (2) psoriasis characteristics; (3) concurrent comorbidities; (4) physical and dermatological examination; (5) laboratory studies.

Patient demographics

Age, gender, place of birth, place of residence was recorded.

Psoriasis characteristics

Age of onset of the disease, existence of nail involvement, age at the onset of nail involvement, type of nail involvement, existence of concomitant PsA, age at the onset of PsA, family history of psoriasis and PsA and age at the onset of psoriasis and PsA of the family member, received treatment regimens and duration of the treatment were recorded. Duration of active psoriatic disease was also required to be evaluated. To make this assessment; active psoriatic disease was defined as existence of cutaneous psoriatic lesions affecting more than 3% of body surface area with or without given treatments and was calculated for each patient. Hospitalizations due to psoriasis and any existed erythroderma attacks were also recorded. Existent or previous psoriatic nail involvement including onycholysis, pitting, subungual hyperkeratosis and oil-drop sign were questioned in detail and recorded. Joint involvement was questioned based on the previous diagnosis of PsA established by a rheumatologist. All patients were also filled out rheumatologic screening questionnaire (RSQ) regarding existence of PsA. RSQ included 5 items: (I) existence of joint and muscle pain at rest, (II) existence of neck, waist or back pain awakening at nights, (III) existence of pain, edema and tenderness in hands or feet joint, (IV) history of morning stiffness lasting for more than 20 minutes, and (V) existence of tenderness while stepping on heels in the mornings [11]. Patients were also consulted to rheumatology department based on the suspicion of PsA according to RSQ (patients with one or more positive answers to 5 items were consulted) and consultation results were added to the study data.

Concurrent comorbidities

Any previous diagnosis of concurrent systemic inflammatory comorbidities comprising HT, DM, NASH, CVD, DLP, MS,
OB was noted. Patients who had physical examination and/or laboratory findings indicative of definite disease according to below mentioned criteria despite lack of previous diagnosis, they were referred to concordant specialist for further evaluation, the results of this consultations were also added to this study data. HT was accepted as having systolic blood pressure ≥ 150 mmHg and diastolic blood pressure ≥ 90 mmHg in patients ≥ 60 years and systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg in patients < 60 years [12]. Fasting blood glucose ≥ 126 mg/dl and random blood glucose ≥ 200 mg/dl was accepted as DM [13]. DLP was defined as total cholesterol levels > 200 mg/dl, LDL cholesterol > 100 mg/dl, HDL cholesterol < 40 mg/dl, TG >150 mg/dl and non-HDL cholesterol > 130 mg/dl, as proposed by American Endocrinology Association [14]. MS was accepted as having any three of the following five criteria: 1. obesity: waist circumference ≥ 102 cm in men and ≥ 88 cm in women; 2. dyslipidemia: TG > 150 mg/dl or having pharmacologic treatment (Rx); 3. dyslipidemia (second, separate criteria): HDL cholesterol < 40 mg/dl in men and HDL cholesterol < 35 mg/dl in women or Rx; 4. HT: systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 85, or Rx; 5. hyperglycemia fasting blood glucose ≥ 100 mg/dl or Rx [15]. CVD included history of MI, coronary artery by-pass surgery, balloon angioplasty or coronary artery stent, cerebrovascular accident or peripheral atherosclerotic vascular disease. OB was defined BMI ≥ 30 [16].

Physical and dermatologic examination
Physical and dermatological examination findings obtained during examination in the last 6 months were noted. Physical examination findings included blood pressure, height, weight and waist circumference. Obtained dermatologic examination results comprised PASI score and affected body surface area (BSA). The severity of psoriasis was classified as mild (BSA ≤ 10; PASI ≤ 10) or moderate-to-severe (BSA > 10 and PASI > 10). Systemic treatment regimen, duration of systemic treatment, duration of active disease (both under treatment and without any treatment), number of erythroderma attacks and hospitalization due to psoriasis were also collected to assess the severity of psoriasis.

Laboratory Studies in EOP and LOP
Laboratory work-up findings of the patients are shown in Table 4. Parameters indicating increased systemic inflammation, eg Red Cell Distribution Width (RDW), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were statistically higher in LOP than in EOP statistically (P = 0.005, P = 0.047 and P = 0.020).

Statistical Analysis
Statistical analysis was performed using Statistical Package for the Social Science (SPSS) version 20.0. Patient group data were presented as mean ± standard deviation (SD) or median (range), as appropriate and compared with adjustments using Fisher exact tests (for categorical variables) and Student two-sample t tests or Wilcoxon rank-sum tests (for continuous variables), subject to normality assumptions being satisfied. Associations between the age at the time of diagnosis and binary comorbidity outcomes were evaluated using multiple logistic regression adjusted for age and other relevant confounders.

Results
Demographic Data and Disease Characteristics in EOP and LOP
Data of 160 patients; 75.62% (N = 121) with EOP and 24.38% (N = 39) with LOP was analyzed and shown in Table 1. Family history of psoriasis was more frequent in EOP significantly. Family history of psoriasis was most frequently positive in the first-degree relatives in EOP and LOP: 23.1%, N = 28 and 10.3%, N = 4, respectively.

Assessment of Severity of Psoriasis in EOP and LOP
Severity of psoriasis was accessed depending on BSA percentage, PASI score, active duration of the disease without any treatment and under treatment, history of hospitalizations due to psoriasis and number of erythroderma attacks and no statistically significant difference was found in any parameters between EOP and LOP (Table 2).

Physical Examination Findings in EOP and LOP
Physical examination findings in EOP and LOP are shown in Table 3. Indicative findings of comorbidities such as HT and OB, eg systolic and diastolic blood pressure and BMI were significantly higher in LOP than in EOP (P = 0.005, P = 0.047 and P = 0.020).

Laboratory Studies in EOP and LOP
Laboratory work-up findings of the patients are shown in Table 4. Parameters indicating increased systemic inflammation, eg Red Cell Distribution Width (RDW), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were statistically higher in LOP than in EOP respectively (P = 0.017, P = 0.006, P = 0.001). Fasting blood glucose was also higher in LOP (P = 0.002).

Systemic Treatments in EOP and LOP
Duration of systemic treatment was 42.09 ± 44.41 months in all patients, 44.41 ± 45.76 in EOP and 34.91 ± 39.65 months in LOP showing no significant difference (P = 0.158).
Table 1. Demographics and family history of psoriasis in EOP and LOP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients (N = 160)</th>
<th>EOP (N = 121)</th>
<th>LOP (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male, N (%)</td>
<td>90 (56.3)</td>
<td>72 (59.5)</td>
<td>18 (46.2)</td>
<td>0.144</td>
</tr>
<tr>
<td>female, N (%)</td>
<td>70 (43.8)</td>
<td>40 (40.5)</td>
<td>21 (53.8)</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean±SD (range)</td>
<td>44.73 ± 13.66</td>
<td>40.46 ±12.24</td>
<td>57.95±8.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at onset of psoriasis, years,</td>
<td>27.24±15.06</td>
<td>20.07±8.45</td>
<td>49.49±7.20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of psoriasis, N (%)</td>
<td>64 (40)</td>
<td>57 (47.1)</td>
<td>7 (17.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

EOP = early onset psoriasis; LOP = late onset psoriasis; SD = standard deviation.

Table 2. Comparison of disease severity in EOP and LOP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients (N = 160)</th>
<th>EOP (N = 121)</th>
<th>LOP (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA, %</td>
<td>3.50 ± 8.65</td>
<td>3.34 ± 8.58</td>
<td>3.99 ± 8.96</td>
<td>0.636</td>
</tr>
<tr>
<td>PASI</td>
<td>3.46 ± 6.42</td>
<td>3.16 ± 6.07</td>
<td>4.37 ± 7.43</td>
<td>0.460</td>
</tr>
<tr>
<td>Active disease without Rx, months</td>
<td>24.46 ± 49.59</td>
<td>28.62 ± 55.26</td>
<td>11.54 ± 20.57</td>
<td>0.083</td>
</tr>
<tr>
<td>Active disease with Rx, months</td>
<td>28.29 ± 68.68</td>
<td>33.78 ± 77.57</td>
<td>11.26 ± 18.32</td>
<td>0.334</td>
</tr>
<tr>
<td>History of hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of positive history, N (%)</td>
<td>28 (17.5)</td>
<td>24 (19.8)</td>
<td>4 (10.3)</td>
<td>0.171</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>0.38 ± 1.25</td>
<td>0.35 ± 0.90</td>
<td>0.49 ± 1.99</td>
<td>0.380</td>
</tr>
<tr>
<td>History of erythroderma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of positive history, N (%)</td>
<td>12 (7.5)</td>
<td>11 (9.1)</td>
<td>1 (2.6)</td>
<td>0.296</td>
</tr>
<tr>
<td>Number of erythroderma</td>
<td>0.13 ± 0.55</td>
<td>0.16 ± 0.61</td>
<td>0.05 ± 0.32</td>
<td>0.187</td>
</tr>
</tbody>
</table>

BSA = body surface area; EOP = early onset psoriasis; LOP = late onset psoriasis; PASI = psoriasis area and severity index; Rx = systemic treatment; SD = standard deviation.

Table 3. Physical examination findings in EOP and LOP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients (N = 160)</th>
<th>EOP (N = 121)</th>
<th>LOP (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm/Hg</td>
<td>118.17 ± 13.39</td>
<td>116.24 ± 12.46</td>
<td>124.18 ± 14.55</td>
<td>0.005</td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(90-160)</td>
<td>(90-150)</td>
<td>(100-160)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm/Hg</td>
<td>79.31 ± 10.94</td>
<td>78.14 ± 10.02</td>
<td>82.95 ± 12.86</td>
<td>0.047</td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(50-120)</td>
<td>(50-100)</td>
<td>(60-120)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.02 ± 4.93</td>
<td>27.62 ± 5.16</td>
<td>29.27 ± 3.94</td>
<td>0.020</td>
</tr>
<tr>
<td>Waist circumference/men, cm</td>
<td>102.07 ± 13.55</td>
<td>101.13 ± 13.97</td>
<td>105.83 ± 11.31</td>
<td>0.190</td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(76-143)</td>
<td>(76-143)</td>
<td>(79-129)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference/women, cm</td>
<td>99.80 ± 13.29</td>
<td>98.67 ± 14.62</td>
<td>102.42 ± 9.29</td>
<td>0.282</td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(76-149)</td>
<td>(76-149)</td>
<td>(84-127)</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; BP = blood pressure; EOP = early onset psoriasis; LOP = late onset psoriasis; SD = standard deviation.
Nail Involvement in EOP and LOP
Psoriatic nail involvement was compared in EOP and LOP, and results are shown in Table 5. The duration of disease between onset of psoriasis and nail involvement was statistically significantly shorter in LOP than EOP (P < 0.01). Duration of active psoriatic disease in patients with nail involvement was also significantly shorter in LOP than in EOP (P < 0.01, P < 0.01).

The most frequent psoriatic nail involvement was seen as pitting, observed in 14% (N = 17) of EOP and 12.8% (N = 5) in LOP. Subungual hyperkeratosis was only observed in 5% (N = 6) of EOP, distal onycholysis was observed in 5% (N = 6) and 10.3% (N = 4), oil-drop sign was observed in 5% (N = 6) and 2.3% (N = 1) of EOP and LOP, respectively.

PsA in EOP and LOP
Data regarding prevalence of PsA, age at onset of PsA, duration between onset of psoriasis and PsA, and active disease duration of patients with PsA with and without treatment are shown in Table 6. Duration between onset of psoriasis and PsA was significantly shorter in LOP than EOP (P < 0.01). Duration of active disease in PsA patients with or without systemic treatments was also significantly shorter in LOP than in EOP respectively (P = 0.002, P < 0.01).

RSQ revealed morning stiffness in 10.7% (N = 13) of EOP and 5.1% (N = 2) of LOP. Muscle-joint complaints were observed in 9.1% (N = 11) and 10.3% (N = 4), small joints complaints were found in 9.1% (N = 11) and 5.1% (N = 2), enthesis complaints were found in 14% (N = 17) and 12.8% (N = 5) and axial complaints were noted in 14.9% (N = 18) and 20.5% (N = 8) of EOP and LOP patients respectively. None of the patients referred to rheumatologic consultations were diagnosed with PsA.

Concurrent Systemic Inflammatory Comorbidities in EOP and LOP
Prevalence and age at onset of systemic inflammatory comorbidities in EOP and LOP are shown in Table 7. CVD, HT, DM and MS were found significantly more frequent in LOP compared to EOP (P = 0.045, P = 0.001, P < 0.01, P = 0.022).

In order to evaluate the effect of psoriasis subtype to the development of concurrent systemic inflammatory comorbidities, multivariate regression analysis was performed; age, gender, severity parameters of disease, alcohol consumption, smoking habits and other concurrent systemic comorbidities were taken into account (Table 8). Based on this analysis, LOP was found as an independent risk factor for CVD and DM (P < 0.01, R²: 0.036; P < 0.01, R²: 0.077). Risk of CVD, DM, HT and MS were increased accordingly with decades of psoriasis onset (P = 0.036, P = 0.007, P = 0.001, P = 0.003). NASH, DLP and OB development risk was not found to be showing this relationship with psoriasis onset (P = 0.194, P = 0.158, P = 0.644).

Conclusions
As it was aimed, comparison of disease characteristics and concurrent inflammatory comorbidities enabled us to spot the peculiar differences in EOP and LOP; we were also able...
Table 5. Psoriatic nail involvement in EOP and LOP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients (N = 160)</th>
<th>EOP (N = 121)</th>
<th>LOP (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail involvement, n (%)</td>
<td>87 (54.3)</td>
<td>68 (56.1)</td>
<td>19 (48.7)</td>
<td>0.415</td>
</tr>
<tr>
<td>Age at nail involvement onset, years</td>
<td>34.29 ± 12.93</td>
<td>29.51 ± 10.23</td>
<td>49.85 ± 7.33</td>
<td></td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(10-70)</td>
<td>(10-62)</td>
<td>(37-70)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Disease duration between Ps and nail</td>
<td>7.4 ± 8.1</td>
<td>9.06 ± 8.5</td>
<td>2.1 ± 3.0</td>
<td>-a, &lt; 0.01b</td>
</tr>
<tr>
<td>involvement, years</td>
<td>mean±SD (range)</td>
<td>(4-37)</td>
<td>(0-37)</td>
<td></td>
</tr>
<tr>
<td>Concurrent nail involvement and PsA, N</td>
<td>28 (17.5)</td>
<td>8 (6.6)</td>
<td>5 (12.8)</td>
<td>0.072 * , 0.041 b</td>
</tr>
<tr>
<td>Active disease duration in patients with</td>
<td>30.63 ± 9.1</td>
<td>35 ± 48.32</td>
<td>16 ± 19.3</td>
<td>0.639 * , &lt; 0.01b</td>
</tr>
<tr>
<td>nail involvement and Rx, months</td>
<td>mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active disease duration in patients with</td>
<td>30.22 ± 9.8</td>
<td>34 ± 50.1</td>
<td>17 ± 18.2</td>
<td>0.027 * , &lt; 0.01 b</td>
</tr>
<tr>
<td>nail involvement without Rx, months</td>
<td>mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EOP = early onset psoriasis; LOP = late onset psoriasis; Ps = psoriasis; PsA = psoriatic arthritis; Rx = systemic treatment; SD = standard deviation. Pa: patients with psoriasis; Pb: between EOP and LOP.

Table 6. PsA characteristics in EOP and LOP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients (N = 160)</th>
<th>EOP (N = 121)</th>
<th>LOP (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA, N (%)</td>
<td>41 (25.6)</td>
<td>33 (27.3)</td>
<td>8 (20.5)</td>
<td>0.057</td>
</tr>
<tr>
<td>Age at PsA onset, years</td>
<td>38.98 ± 11.64</td>
<td>37.0 ± 11.49</td>
<td>47.13 ± 8.77</td>
<td></td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(10-71)</td>
<td>(10-63)</td>
<td>(37-71)</td>
<td>0.025</td>
</tr>
<tr>
<td>Duration between Ps and PsA, years</td>
<td>12.80 ± 11.46</td>
<td>15.72 ± 10.36</td>
<td>0.75 ± 7.36</td>
<td>-a, &lt; 0.01b</td>
</tr>
<tr>
<td>mean±SD (range)</td>
<td>(15-34)</td>
<td>(1-34)</td>
<td>(1-15)</td>
<td></td>
</tr>
<tr>
<td>Active Ps duration in PsA patients with</td>
<td>28.34 ± 9.2</td>
<td>34 ± 20.1</td>
<td>6 ± 8.3</td>
<td>0.761 * , 0.002b</td>
</tr>
<tr>
<td>Rx, months</td>
<td>mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Ps duration in PsA patients</td>
<td>27.98 ± 10.3</td>
<td>33 ± 15.1</td>
<td>9 ± 18.1</td>
<td>0.803 * , &lt; 0.0 b</td>
</tr>
<tr>
<td>without Rx, months</td>
<td>mean±SD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EOP = early onset psoriasis; LOP = late onset psoriasis; Ps = psoriasis; PsA = psoriatic arthritis; Rx = systemic treatment; SD = standard deviation. Pa: patients with psoriasis; Pb: between EOP and LOP.

to evaluate the sole contribution of psoriasis subtype (LOP) to the developmental risk of certain comorbidities determined as CVD and DM.

Psoriasis is proven to cause serious systemic inflammation however the exact tools to monitor the inflammatory burden is yet to be discovered. Reports in literature concerning the severity of psoriasis subtypes comparing EOP and LOP are few and contradictory. In these data, authors mostly used PASI score, BSA and duration of systemic treatment to evaluate severity of psoriasis. Although some researches did not find significant difference in the severity of psoriasis between EOP and LOP, others found EOP to be more severe than LOP [1,3,4,7,17]. In this study, evaluation of psoriatic inflammation was assessed by severity parameters along with calculations made for active disease duration and duration of time between onset of psoriasis and concurrent inflammatory comorbidities. Although traditional markers of psoriasis severity such as PASI scores and BSA did not show any difference between EOP and LOP, we found that LOP was associated with rapid development of psoriatic nail involvement and PsA in statistically significantly shorter periods of time despite shorter active disease durations with and without treatment. LOP was also found to associate with higher levels of inflammatory serum markers like CRP, ESR and RDW. As a whole, our results strongly support that LOP poses heavier and rapid inflammatory burden. Accordingly, we prioritize the determination of the disease subtype as EOP or LOP and suggest exploring the duration of time between...
Table 7. Prevalence and age at onset of psoriatic comorbidities in EOP and LOP

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients (N = 160)</th>
<th>EOP (N = 121)</th>
<th>LOP (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD, N (%)</td>
<td>4 (2.5)</td>
<td>1 (0.8)</td>
<td>3 (7.7)</td>
<td>0.045</td>
</tr>
<tr>
<td>Age at CVD onset, years</td>
<td>50.75 ± 2.36</td>
<td>51</td>
<td>50.67 ± 1.67</td>
<td>0.929</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>32 (20)</td>
<td>17 (14)</td>
<td>15 (38.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at HT onset, years</td>
<td>44.28 ± 8.23</td>
<td>41.53 ± 5.37</td>
<td>47.40 ± 9.87</td>
<td>0.165</td>
</tr>
<tr>
<td>DM, N (%)</td>
<td>25 (15.6)</td>
<td>12 (9.9)</td>
<td>13 (33.3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age at DM onset, years</td>
<td>42.68 ± 9.79</td>
<td>37.75 ± 7.70</td>
<td>47.23 ± 9.53</td>
<td>0.004</td>
</tr>
<tr>
<td>NASH, N (%)</td>
<td>29 (18.1)</td>
<td>22 (18.2)</td>
<td>7 (17.9)</td>
<td>0.974</td>
</tr>
<tr>
<td>Age at NASH onset, years</td>
<td>39.21 ± 8.20</td>
<td>37.48 ± 8.34</td>
<td>44.43 ± 5.38</td>
<td>0.045</td>
</tr>
</tbody>
</table>
| CVD = cardiovascular disease; DLP = dyslipidemia; DM = diabetes mellitus; EOP = early onset psoriasis; HT = hypertension; LOP = late onset psoriasis; MS = metabolic syndrome; NASH = non-alcoholic steatohepatitis; OB = obesity; SD = standard deviation.

Table 8. Multivariate regression analysis of impact of psoriasis subtype on concurrent systemic inflammatory comorbidities

<table>
<thead>
<tr>
<th>Variables</th>
<th>HT</th>
<th>DM</th>
<th>IBD</th>
<th>NASH</th>
<th>CVD</th>
<th>DLP</th>
<th>MS</th>
<th>OB</th>
<th>Rx duration</th>
<th>Disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT</td>
<td>-</td>
<td>0.158</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.249</td>
<td>0.225</td>
<td>0.177</td>
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<tr>
<td>DM</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-0.167</td>
<td>-</td>
<td>0.235</td>
<td>-</td>
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</tr>
<tr>
<td>IBD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.217</td>
<td>-</td>
</tr>
<tr>
<td>NASH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.219</td>
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</tr>
<tr>
<td>CVD</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-0.557</td>
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<tr>
<td>DLP</td>
<td>-0.231</td>
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<td>-</td>
<td>-</td>
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<td>MS</td>
<td>0.402</td>
<td>0.309</td>
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<tr>
<td>OB</td>
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<td>0.220</td>
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<tr>
<td>PASI</td>
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<td>-</td>
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<tr>
<td>BSA</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Ps subtype</td>
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<td>-</td>
<td>-</td>
<td>-0.747</td>
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<tr>
<td>Gender</td>
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<td>-</td>
<td>-0.265</td>
<td>-0.163</td>
<td>-</td>
<td>0.182</td>
<td>-</td>
<td>0.101</td>
</tr>
<tr>
<td>Duration of Rx</td>
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<td>0.236</td>
<td>0.250</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-1.009</td>
<td>0.663</td>
</tr>
<tr>
<td>Age</td>
<td>0.403</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.224</td>
<td>-</td>
<td>-</td>
<td>1.009</td>
<td>0.663</td>
</tr>
<tr>
<td>Disease duration</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.516</td>
<td>-</td>
</tr>
<tr>
<td>Duration of active disease without Rx,</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>0.156</td>
</tr>
<tr>
<td>Duration of active disease with Rx</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.123</td>
<td>-</td>
<td>-</td>
<td>0.188</td>
</tr>
<tr>
<td>Smoking</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>R² Value</td>
<td>0.288</td>
<td>0.237</td>
<td>0.056</td>
<td>0.200</td>
<td>0.133</td>
<td>0.451</td>
<td>0.538</td>
<td>0.115</td>
<td>0.325</td>
<td>0.620</td>
</tr>
<tr>
<td>P Value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.003</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

BSA = body surface area; CVD = cardiovascular disease; DLP = dyslipidemia; DM = diabetes mellitus; HT = hypertension; IBD = inflammatory bowel disease; MS = metabolic syndrome; NASH = non-alcoholic steatohepatitis; OB = obesity; PASI = psoriasis area and severity index; Ps = psoriasis; Rx = systemic treatment.
onset of psoriatic involvements and comorbidities (psoriatic nail, PsA, CVD, DM, HT, MS) and active disease duration for evaluating inflammation and its consequences in psoriasis. We believe that the all-together analysis of these parameters with the traditional clinical severity scores may create a new concept of approach for psoriasis follow-up.

Nail involvement is observed in 13%-50% of psoriasis patients and this rate increases to 80%-90% by age [18]. Reports on nail involvement in EOP and LOP differ; some report more frequent nail involvement in EOP, others found that LOP more frequently affect nails [3,5,10,17]. There are also studies showing no difference in nail involvement between EOP and LOP [1,4,7]. We did not observe statistically significant difference in both nail involvement and type of nail involvement, neither. But interestingly, nails were found to be affected in significantly shorter duration in LOP in comparison with EOP. Similar to the findings observed in psoriatic nail involvement, PsA was found to develop in significant shorter periods of time in EOP. Generally, PsA is observed in 5-30% of patients with psoriasis [19]. Most researches did not find difference in concurrent PsA between EOP and LOP [3,4,7]. Heredi et al have demonstrated that the PsA was more frequent in EOP and risk of development of PsA decreases by increasing age and this risk completely disappears after age 75 [1]. In this study, there was no difference between EOP and LOP for associating PsA prevalence. RSQ responses were also similar in two disease subtypes. As it leads to PsA faster than EOP, LOP can be accepted to generate a rapid inflammatory course and cause damage target organs such as nails, ligaments, tendons and joints.

Increased frequencies of systemic comorbidities such as CVD, DM, HT and MS in LOP compared to EOP were detected in this study. BMI, systolic and diastolic blood pressure values, fasting blood glucose, BUN, CRP, ESR, RDW levels were also higher in LOP. These findings suggest that concomitant inflammatory comorbidities may increase the amount and speed of psoriatic inflammation. To our knowledge there are no reports comparing the laboratory indicative of systemic inflammation in EOP and LOP, but these parameters have been shown to be higher in psoriasis patients in comparison to general population [20,21]. RDW and CRP levels have also been suggested as reliable markers of inflammation in psoriasis [20,21]. Besides, elevated levels of CRP have been shown to be an independent risk factor for development of CVD in psoriasis and may be associated with increased risk of MS [21]. However, there is again few data of psoriasis subtype and its contribution to these concurrent comorbidities. Heredi et al did not found difference in the risk of development of CVD between EOP and LOP [1]. Despite our low number of cases in the study, LOP was able to be shown as an independent risk factor for CVD and DM. This risk must be kept in mind in LOP and on time referral and adequate anti-psoriatic treatment choice is mandatory and is lately recommended in psoriasis guidelines [22].

EOP and LOP are two different types of psoriasis with different etiologies, clinical characteristics, laboratory indicatives and concurrent systemic comorbidities. Despite similar treatment regimens and shorter duration of active disease, LOP causes faster nail and joint involvement in a shorter period of time and is more frequently associated with systemic inflammatory comorbidities such as CVD, DM, HT and MS. LOP was also found to be independent risk factor for development of CVD and DM. From this aspect, we prioritize the determination of the disease subtype as EOP or LOP and suggest LOP to be closely monitored for potential development of end-organ inflammatory comorbidities. LOP must be considered as the more rapid and aggressive type of psoriasis which provokes development of inflammatory comorbidities in shorter duration in comparison to EOP.

References


Comparison of Convolutional Neural Network Architectures for Robustness Against Common Artefacts in Dermatoscopic Images

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Key words: image classification, object detection, instance segmentation, artefacts, dermatoscopy,

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Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Classification of dermatoscopic images via neural networks shows comparable performance to clinicians in experimental conditions but can be affected by artefacts like skin markings or rulers. It is unknown whether specialized neural networks are more robust to artefacts.

Objectives: Analyze robustness of 3 neural network architectures, namely ResNet-34, Faster R-CNN and Mask R-CNN.

Methods: We identified common artefacts in the HAM10000, PH2 and the 7-point criteria evaluation datasets, and established a template-based method to superimpose artefacts on dermatoscopic images. The HAM10000-dataset with and without superimposed artefacts was used to train the networks, followed by analyzing their robustness against artefacts in test images. Performance was assessed via area under the precision recall curve and classification results.

Results: ResNet-34 and Faster R-CNN models trained on regular images perform worse than Mask R-CNN on images with superimposed artefacts. Artefacts added to all tested images led to a decrease in area under the precision-recall curve values of 0.030 for ResNet-34 and 0.045 for Faster R-CNN in comparison to only 0.011 for Mask R-CNN. However, changes in model performance only became significant with 40% or more of the images having superimposed artefacts. A loss in performance occurred when the training was biased by selectively superimposing artefacts on images belonging to a certain class.

Conclusions: As Mask R-CNN showed the least decrease in performance when confronted with artefacts, instance segmentation architectures may be helpful to counter the effects of artefacts, warranting further research on related architectures. Our artefact insertion mechanism could be useful for future research.
Introduction

Epidemiological studies show an increasing trend in the incidence rates of melanoma and non-melanoma skin cancer worldwide over the last 30 years [1]. According to the American Joint Committee on Cancer melanoma staging system, stage I malignant skin alterations with a five-year survival rate of more than 90% contrasts with a survival rate of less than 15% for stage IV patients. This indicates a clear need for early, reliable and consistent diagnosis and treatment [2]. The desire for automatic lesion analysis is further intensified by a high dependency between the diagnostic quality and the examiners experience in dermoscopy, as well as a high degree of inter- and intra-variability of diagnoses [3,4].

Methods of automatic skin lesion analysis have been the focus of research for decades, and have gained interest in recent years [5,6]. These methods are intended to support tele-dermatologic settings, improve management decisions or aid in difficult clinical scenarios, but often suffer, among other things, from the presence of artefacts in dermatoscopic images [7-12].

A common neural network used for classification is ResNet, two well-known neural network architectures in computer vision are Faster R-CNN and Mask R-CNN (Figure 1) [13,14]. The first is performing “object detection”, a process where one or multiple objects in an image can be detected and located with a rectangular “bounding box”. The latter is performing “instance segmentation” where one or more objects in an image can be found and their respective area (i.e. pixels) in the image outlined (“segmented”), and can be regarded as a CNN-based multi-instance generalisation of computer-vision based techniques of lesion segmentation [15,16]. Object detection has been used in the field of automated skin cancer detection on clinical images [17], but training of instance segmentation neural networks in dermatoscopy has not yet been reported on successfully, most probably because of missing ground-truth data.

Objectives

Our hypothesis is that in contrast to ResNet, the other network architectures intrinsically have to “concentrate” on regions of the classified object in an image and hence may offer robustness against artefacts surrounding the lesions. Robustness in this case describes the consistency of the obtained diagnoses under the influence of artefacts in the input image data. These networks could potentially be used as off-the-shelf methods with little customization-effort needed and could enable us to focus less on tedious image pre-processing such as removal of bubbles or hairs [18].

Methods

Image datasets

The primary source of dermatoscopic images was the HAM10000 dataset [19]. This dataset also includes publicly available lesion segmentation masks for every image, as described previously, which are necessary for training the Faster R-CNN and Mask R-CNN architectures [8]. It contains 10,015 images, each with 600x450 pixels and 3-8 bit color channels. Each image is assigned one of seven diagnostic classes: actinic keratosis / intraepithelial carcinoma

![Figure 1. A visual representation of the outputs of the three approaches. Image classification (ie ResNet-34) classifies the image as a whole, object detection (ie Faster R-CNN) finds objects and their approximate position in the image and instance segmentation (ie Mask R-CNN) finds objects and their exact spatial delimitation.](image-url)
(akiec), basal cell carcinoma (bcc), benign keratotic lesion (bkl), dermatofibroma (df), nevus (nv), melanoma (mel), or vascular lesion (vasc). Also, the PH2 and the 7-point criteria evaluation dataset were reviewed and several images were utilized to extract artefacts from [20,21]. Images from those datasets were not used for other purposes within this study. We used the ISIC2018 test-set as the test-set to keep variation as low as possible, as it sources from the same origin as the HAM10000 dataset and includes the same classes.

**Artefact generation**

As with every real-world picture, dermatoscopic images can contain content considered as “artefacts”. Examples are hairs, dark corners, vignettes, medical devices, different sorts of rulers, ink markings in different shapes, styles and colors, air bubbles or reflections. This work focuses on three of them: “bubbles” that originate from trapped air in the liquid between skin and the dermatoscope, “rulers” used to show the spatial dimension of a lesion, and ink “markings” on the patient’s skin used to highlight the lesion for excision or review.

In order to generate artefact-modified cases, we selected 60 images from the HAM10000, PH2 and 7-point criteria dataset which contain either a bubble, a ruler or a marking artefact. From those images we extracted the artefacts by manually repairing the images areas with Adobe® Photoshop’s® (version CC 2018 (19.1.9), Adobe Inc.) content aware image repair mechanism and using the difference, per RGB channel, to the untouched image as a template (Figure 2). The insertion of those templates was done in a way that the position of artefacts varies according to observed patterns, using the provided segmentation mask of the target image. In Figure 3, a dermatoscopic image with automatically superimposed artefacts is shown. The source code will be made available upon publication of this work at https://github.com/thisismexp/artefact_insertion.

Using the artefact insertion mechanism, several dataset mutations of the original HAM10000 dataset were created, where artefacts were superimposed on either none or all of the images and on every image belonging to a certain diagnosis. The test portion of the HAM10000 dataset, corresponding to the ISIC2018 challenge Task 3 test-set with 1,511 images, was altered in the same way. Additionally, artefacts were inserted in a certain percentage of images in 20% step increments.

**Neural Network Training**

As representatives for image classification, object detection and instance segmentation we trained a ResNet-34, a Faster...
R-CNN (with ResNet-34 backbone) and a Mask R-CNN (also with a ResNet-34 backbone) model as provided by the Torchvision package of the open source machine learning framework PyTorch [22]. All models were trained on all of the 9 generated datasets in a 5-fold cross validation fashion. Transfer-learning and data augmentation including random crops, resize, rotations, mirroring operations as well as color jitter operations were used.

Statistics

To evaluate diagnostic accuracy, all trained network models are tested against the 13 test datasets and performance was reported in terms of area under the precision recall curve (PR-AUC), precision, recall, false positive (FPR) and false negative rates (FNR) and differences thereof (calculated using scikit-learn version 0.24.1) [23]. To visualize spatial activations, Gradient based Class Activation Map (Grad-CAM) visualizations were used. A two-sided p-value of 0.05 was regarded as statistically significant, and all calculations were performed using statsmodels version 0.12.2 [24].

Results

Baseline performance in terms of PR-AUC of our models trained and tested with no additional artefacts was 0.8 for ResNet-34 and 0.72 for Faster R-CNN as well as Mask R-CNN. Introduction of artefacts in only the test dataset led to a reduction in performance for all three architectures (Figure 4) increasing with the proportion of artefacts present in the test dataset, and more severe for the ResNet-34 and Faster R-CNN model. With a maximum relative reduction of 0.05 PR-AUC the Faster R-CNN model was affected the most, ResNet-34 (-0.03) the second most, and Mask R-CNN was the most robust (-0.01). For ResNet-34 and Faster R-CNN, changes in predictive performance compared to baseline was significant at and above 40% of introduced artefacts in the test set (P < 0.01; tested using McNemar test with Edwards correction on binarized predictions). For Mask R-CNN we did not detect a significant difference in predictions in all used test sets (all P values > 0.17).

Introducing artefacts in the training data led to biased results in all three examined architectures. Artefacts introduced
into all images of the melanocytic nevi class during training decreased recall values on average by 0.218 for ResNet-34, 0.129 for Faster R-CNN and by 0.155 for Mask R-CNN in comparison to the respective unbiased models. Reduction in recall values indicate that those are indeed biased by artefacts for specific classes. This effect was more apparent the bigger the proportion of biased samples in the dataset is. Considering the FPR and FNR for specific classes, a selective bias towards classes that were corrupted by artefacts during training could be observed for all three architectures. The increase in FPR for the class with inserted artefacts during training, and a simultaneous increase in FNR for all others, in fact showed a shift in classifications towards the biased class. This effect could not be observed if artefacts were inserted into none or all of the images.

When inspecting heat map representations of the Grad-CAM we observed that training with artefacts shifted the attention of the object detection and instance segmentation network away from the artefact itself towards areas of the lesion (Figure 5). These mappings indicate an increase in robustness against these very artefacts for Faster and Mask R-CNN models, if trained with inserted artefacts in the dataset.

![Figure 5](image.png)

**Figure 5.** Grad-CAM for used network architectures. The first column shows the input image for the corresponding row, in its original form (top) and with bubble artefacts inserted (bottom). Grad-CAM heatmaps show the ResNet-34 increases attention towards the bubble-area after training with artefacts (N), where the Faster R-CNN network loses its initial attention towards the artefact (G) afterwards (O). The Mask R-CNN architecture seems to ignore the artefact throughout (H and P). Black boxes denote positions of inserted bubble artefacts.
Conclusions

We compared representatives of three neural network architectures to classify lesions in dermoscopic images in regard to their robustness against artefacts. Although as a limitation the baseline performance of the examined models were not the same, we found differences in their vulnerability to performance changes under the influence of artefacts. Mask R-CNN tends to be the most robust. The influence on classification results by artefacts in test images can be reduced by augmenting training data with artificially superimposed artefacts for all three architectures. This is in line with findings by Maron et al, who reduced - but not eliminated - brittleness of their system through data augmentation [25]. We anticipate that automated superimposition of artefacts as presented here as a further evolution of data augmentation, that together with integrating more diverse variants, will enhance robustness of automated classifiers and decision support systems further [26,27]. The initial data, in our view, warrants more in-depth follow up research on this topic, to understand which approaches are the most effective and efficient.

However, this work failed to find evidence for a clinically relevant robustness against artefacts of instance segmentation for several reasons. On the one hand we used a shallow backbone network architecture for our experiments, even though current research and commercial products commonly use deeper models, and an increase in robustness against image distortions has been demonstrated by others with increased backbone capacity [28]. We also used a new template-based approach to superimpose artefacts on images. This approach leaves room for improvement with regard to the number of images the artefacts are extracted from, and a detailed analysis on how different artefact types affect the classification performance. Alternatively, lesions with existing artefacts could be used after manual or automated annotations.

References


Introduction: Improving remote triage is crucial given expansions in tele-dermatology and with limited in-person care during COVID-19. In addition to clinical pictures, dermoscopic images may provide utility for triage.

Objectives: To determine if dermoscopic images enhance confidence, triage accuracy, and triage prioritization for tele-dermatology.

Methods: In this preliminary parallel convergent mixed-methods study, a cohort of dermatologists and residents assessed skin lesions using clinical and dermoscopic images. For each case, participants viewed a clinical image and determined diagnostic category, management, urgency, and decision-making confidence. They subsequently viewed the associated dermoscopy and answered the same questions. A moderated focus group discussion followed to explore perceptions on the role of dermoscopy in tele-dermatology.

Results: Dermoscopy improved recognition of malignancies by 23% and significantly reduced triage urgency measures for non-malignant lesions. Participants endorsed specific utilities of tele-dermoscopy, such as for evaluating pigmented lesions, with limitations including poor image quality.

Conclusions: Dermoscopic images may be useful when remotely triaging skin lesions. Standardized imaging protocols are needed.
Introduction

Tele-dermatology plays an important role in triage of potentially malignant skin lesions. Tele-dermatology has comparable diagnostic accuracy to in-person evaluations, though, study results vary for malignant lesions [1]. The use of dermoscopic images, in addition to clinical images, can improve accuracy, especially for pigmented skin cancers [2-5].

Images are imperative for the remote management of skin lesions. Prior to the COVID-19 pandemic, many primary providers would arrange to have patient images taken by trained in-office personnel, which are then used for store-and-forward tele-dermatology. There is also an increasing demand for patients to submit photographs of their skin problems without needing to go to the primary care office at all. COVID-19 realized the difficulty of patients to have their skin lesions imaged in person. Dermatologists are then faced with using patient-provided images taken with smartphones or computers [6,7]. The quality of these images is variable. Dermoscopic images have become almost universally unavailable. While the social restrictions resulting from the COVID-19 pandemic are loosening, remote patient care has become a possible parallel care paradigm. Thus, to adequately triage patients and maintain high standards of care, innovative means are required to ensure access to high quality images, including assessing the added value of dermoscopy [1,6,8,9].

Objectives

Our preliminary study aims to assess the impact of dermoscopic images on providers abilities to classify and triage skin lesions, and on their confidence in their decision making. We implemented a parallel convergent mixed method design to quantify the utility of dermoscopy for remotely triaging skin lesions and to assess providers’ perceptions of dermoscopy as a triage tool in tele-dermatology.

Methods

Study Design and Data Collection

A convergent parallel mixed-methods design was used to collect, analyze, and interpret quantitative and qualitative data. The study was approved by the Institutional Review Board at Emory University and the Atlanta Veterans Affairs Medical Center Research and Development committee. The Veteran Integrated Service Network (VISN) 7 TeleDermatology service serves as a reading hub for the community-based out-patient clinics (CBOCs) in Atlanta as well as for other VISN 7 medical centers. Imagers are trained by the tele-dermatology service to take photographs per standard protocol established by the VA National TeleDermatology Service: a forest view, and close-up, and a dermoscopic view are taken for every lesion and rash. There is not mandated specific magnification or lighting. Images are uploaded via VistA Imaging, an FDA-listed Image Management system employed by Department of Veterans Affairs healthcare facilities nationwide. To maintain our imaging quality standards, feedback for image quality is given for each consult (fully satisfactory, satisfactory with suggestions, and unsatisfactory). For the present study, images from tele-dermatology consults received between 12/1-31/2018 were reviewed. Twenty sets of clinical and dermoscopic images were selected as representative of common benign and malignant skin lesions seen in the tele-dermatology clinic. Diagnoses for malignant lesions were confirmed with biopsy. Benign lesions were classified by consensus among tele-dermatology providers. Clinical and dermoscopic images were de-identified and compiled into a digital slide show using Microsoft PowerPoint Version 16.55. High image quality was maintained at 300 dots per inch.

This preliminary study was conducted over a two-day period using Zoom, a video communication platform with a built-in polling function. Participants filled out a demographic survey, including a series of questions relating to their use of dermoscopy in their clinical practices, prior dermoscopic training, and overall confidence in their dermoscopic abilities. They were shown a clinical image of a skin lesion or multiple skin lesions and asked to determine diagnostic category, management decision (reassure versus further in-person management), perceived level of urgency with which further action is required (not urgent, urgent, emergent), and self-rated confidence level in their decision making (range from 0% to 100% confidence in intervals of 10 percentage points) (Supplemental Material, Survey). Diagnostic categories included non-neoplastic (folliculitis, epidermal inclusion cyst, verruca; 3/20 cases), benign neoplastic (actinic keratosis, seborrheic keratosis, blue nevus, sebaceous hyperplasia, dermatofibroma, melanocytic nevus, angioma; 11/20 cases), and malignant neoplastic (melanoma, basal cell carcinoma, squamous cell carcinoma; 6/20 cases). These images are supplied in Supplemental Table 1. Participants were then shown the accompanying dermoscopic image and asked the same questions. This process was repeated for all twenty study sets. On study day two, a moderated group discussion took place in which participants were asked questions pertaining to their perception of the utility of dermoscopic images for triaging skin lesions and if the Covid-19 pandemic has changed these perceptions (Supplemental Material, Debriefing prompts). The discussion was recorded and transcribed verbatim.

Data Analysis

GraphPad Prism 6 (GraphPad Software) was used for statistical analysis and graphic presentation of survey results. Paired t-tests were used to compare differences in confidence...
and correct diagnosis before and after revealing dermoscopic images. Survey data were expressed as means with 95% confidence interval. For urgency and management, McNemar’s test was used to determine statistical significance in differences between the ratings before and after exposure to dermoscopic images. To test whether confidence was correlated with correct diagnoses, we used a regression analysis over the average self-rated confidence and average percentage of correct diagnoses per provider. Results were considered significant if P resulted < 0.05. For qualitative analysis of the participant comments, 2 study investigators (TR, MRM) independently reviewed and coded the entire transcript from the group discussion. Themes were developed inductively and defined as having at least three study participants having similar responses to the study questions. Investigators consolidated these comments into a list of key themes designed to characterize perceived benefits, potential applications, and shortcomings of dermoscopic images for remotely triaging skin lesions. Discrepancies were resolved by consensus.

Results

Demographics

Twenty-six physicians participated in this preliminary study, including 16 dermatology attendings and 10 residents (Table 1). Attending physicians had a wide spread of years in practice. Half of survey participants reported using dermoscopy in ≥50% of their clinical practice. Over half (55%) reported having attended at least one formal dermoscopy course. When asked about their confidence in their dermoscopic abilities, 59% of study participants indicated that they were “somewhat confident” using dermoscopy. None of the study participants were “confident” in their dermoscopic abilities.

Survey Results

Using clinical images alone, 45% of physicians (12/26) correctly diagnosed the study cases. (This increased to 53% (14/26) after viewing the associated dermoscopic images (P = 0.02, paired t-test) (Figure 1). The greatest increase was for malignant neoplasms (31% [8/26] versus 54% [14/26], P = 0.0007).

After showing clinical images, 54% (14/26) rated non-neoplastic lesions (ie, inflammatory and infectious) as “non-urgent”, which significantly increased to 81% (21/26) after viewing the associated dermoscopic images (P < 0.0001, McNemar test) (Figure 2). There was a trend to reduce urgency for benign neoplastic lesions (from 69% to 78% non-urgent) and increase urgency for malignant neoplastic lesions (from 44% to 58% urgent/emergent) following dermoscopic images. With regards to management decisions, significantly more providers opted to provide reassurance (14/26) rather than interventions (0/26) for non-neoplastic lesions following the addition of dermoscopic images (P < 0.0001). The addition of dermoscopy did not lead to significant changes in management for benign or malignant neoplastic lesions.

We found a 7.6% increase in providers’ confidence in their management decisions with dermoscopy (P < 0.0001) (Figure 3). There was also a weak but statistically significant (r² = 0.246 P = 0.024) correlation between providers level of confidence and correct diagnoses.

Theme Results

We conducted a thematic analysis of the moderated discussion on the role of dermoscopy for triage during COVID-19 (Table 2). The first theme involved the specific utilities of dermoscopy. Participants endorsed that dermoscopy was useful for suspected malignancy, pigmented lesions, lesions with well-known dermoscopic features, and in conjunction with patient history, and less useful for generalized exanthems. The second theme was image quality. Many voiced that image quality for both clinical and dermoscopic images was critical and often a major limitation. Thirdly, participants commented on accessibility to dermoscopy during the coronavirus pandemic, and also with technological advances and expansions in telehealth. Notably, providers felt that

<table>
<thead>
<tr>
<th>Characteristics, N (%)</th>
<th>Completed Survey</th>
<th>Status</th>
<th>Attending</th>
<th>Years in practice (Attendings)</th>
<th>% Clinical practice using dermoscopy</th>
<th># Formal dermoscopy courses</th>
<th>Level of confidence in dermoscopy skills</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22/26 (84.6%)</td>
<td></td>
<td>16/26 (61.5%)</td>
<td>4/13 (31%)</td>
<td>13/26 (50%)</td>
<td>10/22 (45.5%)</td>
<td>9/22 (40.9%)</td>
</tr>
</tbody>
</table>
Our preliminary findings demonstrate that dermoscopy can be a useful adjunct when remotely triaging skin lesions. This finding corroborates previous studies that suggest dermoscopic images improve recognition of neoplastic lesions, particularly for pigmented lesions such as melanoma.

Thematic analysis of the moderated discussion revealed that providers feel dermoscopic images are most useful for triaging malignant lesions and pigmented lesions, specifically those with the most common morphological features. Interestingly, despite improving providers’ abilities to correctly classify malignant neoplastic lesions (Figure 1), the addition of dermoscopy did not significantly affect urgency scores or management decisions. This may reflect the lack of consensus amongst providers on the perceived urgency for treating slow growing malignancies such as basal cell carcinoma [15].

While training may be a limiting factor for the usefulness of dermoscopic images, study participants also voiced concerns about the impact of image quality. The success of the VISN 7 tele-dermatology program is in part due to imaging protocols that ensure consistently high image quality. This involves staff training, imaging equipment, and additional time—investments that are required for the success of future tele-dermatology efforts [16].

Our moderated discussion also revealed that participants do not find dermoscopy useful for triaging widespread skin

Conclusions

Our preliminary findings demonstrate that dermoscopy can be a useful adjunct when remotely triaging skin lesions. This finding corroborates previous studies that suggest dermoscopic images improve recognition of neoplastic lesions, particularly for pigmented lesions such as melanoma. Our results indicate that dermoscopy may have additional utilities. Specifically, we found that dermoscopy reduced provider perception of urgency for benign lesions such as verruca (Figure 2). Consequently, a greater proportion of dermatologists in our study opted against prioritizing these patients for in-person evaluation. This is important in the setting of the COVID-19 pandemic, as the risk of viral exposure must be balanced with the benefits of office visits. Additionally, tele-dermoscopy may allow for better resource utilization [14]. The ability to reduce the number of in-person visits allows for the care of a greater volume of patients and prevents unnecessary travel.

Reduced access to dermoscopy during COVID-19 hampered tele-dermatology efforts. However, there was hesitancy towards direct-to-consumer dermoscopy.
Table 2. Perceptions of dermoscopy for triage in tele-dermatology described by study participants, presented by theme and subtheme with exemplary quotes.

<table>
<thead>
<tr>
<th>Theme and Subtheme</th>
<th>Exemplary Quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of dermoscopy</td>
<td></td>
</tr>
<tr>
<td>Useful for suspected malignancy and pigmented lesions</td>
<td>“Dermoscopy can be very useful for lesions suspicious for malignancy.”</td>
</tr>
<tr>
<td></td>
<td>“(Dermoscopy) has a lot to add for pigmented lesions and neoplasms.”</td>
</tr>
<tr>
<td>Useful for lesions with common dermoscopic morphologies</td>
<td>“Clear features can increase confidence; more obscure structures are less helpful.”</td>
</tr>
<tr>
<td></td>
<td>“There are certain things that I can trust dermoscopy for, like single lesions with specific findings.”</td>
</tr>
<tr>
<td>Less useful for rashes (of note, there were no rashes included in the survey)</td>
<td>“Dermoscopy for limited portions of an exanthem, especially without history, can be misleading.”</td>
</tr>
<tr>
<td></td>
<td>“Clinical images are more reassuring and less confusing than dermoscopy for rashes.”</td>
</tr>
<tr>
<td>Patient history complements dermoscopic images</td>
<td>“I want to know the patient’s problem list and how acute this is relative to other comorbidities.”</td>
</tr>
<tr>
<td></td>
<td>“For example, if I see that this patient is immunosuppressed on the primary care note, that will change things.”</td>
</tr>
<tr>
<td>Importance of image quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“If you have protocols for taking photos outlined, then that is more helpful. For the most part it’s going to be patients and nurses taking photos, so we need good protocols and feedback mechanisms in place, so protocols are followed.”</td>
</tr>
<tr>
<td></td>
<td>“The lack of utility is based on both photo quality (such as extreme close ups, blurriness, lighting), as well as not knowing what to take photos of.”</td>
</tr>
<tr>
<td>Increased accessibility to dermoscopy</td>
<td></td>
</tr>
<tr>
<td>COVID19 limited availability to dermoscopic images</td>
<td>“I felt handicapped [during COVID19] for neoplastic lesions, dermoscopy is crucial for those.”</td>
</tr>
<tr>
<td></td>
<td>“[The transition to teledermatology during COVID19] has made me realize the limitations of webcam and poor-quality images, which makes imaging protocols more important.”</td>
</tr>
<tr>
<td>Hesitancy for consumer dermoscopy</td>
<td>“I also worry that people might think they can interpret [dermoscopic images], which might be a problem. Even medical students don’t get formal training in dermoscopy.”</td>
</tr>
<tr>
<td></td>
<td>“I’m skeptical about this technology in the hands of patients, but there might be utility for our high risk pigmented lesion patients.”</td>
</tr>
</tbody>
</table>

eruptions. They feel that it would save time and resources to have primary providers submit dermoscopic images only for appropriate cases. However, having primary providers or patients determine which cases require dermoscopic images is asking them to decipher skin eruptions from discrete skin lesions. In the present study, we included two cases in which field actinic keratoses and field sebaceous hyperplasia were misidentified by the referring primary provider as generalized exanthems (Supplemental Table 1). It has been shown that primary care providers have difficulty diagnosing field actinic keratoses [17]. Accordingly, the tele-dermatology imaging protocol at the VISN 7 Teledermatology service requires clinical and dermoscopic images for every consult. While this requires more time and resources, it eliminates the possibility for this type of error. The ideal imaging protocol is likely dependent on resources available at specific institutions. A previous study of digital imaging for tele-dermatology suggests that standardization should involve a panoramic photo, a close-up with measurements, and a dermoscopic image [18].

Our study participants had a wide and varied range of dermoscopy training and utilization in clinical practice (Table 1). While most (55%) of participants in our survey had training with at least 1 formal dermoscopy course, few dermatology residency programs provide formalized dermoscopy training [19]. In the present study, participants had low self-reported confidence in their dermoscopic abilities, despite some with extensive use in their clinical practice. This may be attributed to the varying utilities of dermoscopy in different contexts, for example, where participants felt dermoscopy was less useful for rashes (Table 2). The addition of dermoscopy, nonetheless, proved useful for correctly triaging benign and malignant skin lesions. These results and others suggest the benefits of dermoscopy could justify a standardized curriculum to be used across residency programs. This educational gap must be addressed so that rising dermatologists are able to confidently use dermoscopy to its full potential [20-23].

Our discussion revealed that providers are hesitant about consumer dermoscopy. There is concern that patients might start interpreting their own images, placing them at risk for mismanagement. This concern has been voiced by others as well [24]. However, studies have indicated that
patient-performed tele-dermoscopy are both desirable for patients and effective [25-27]. For direct-to-patient tele-dermatology to become a viable paradigm, taking dermoscopic images needs to be foolproof and economical. Efforts are underway to address these criteria with user-friendly, affordable dermoscopes and smart phone attachments [7, 28]. Care must be taken to ensure adequate instruction.

An additional consideration is the rapid and effective classification of dermoscopic images using artificial intelligence (AI). Recent reviews have highlighted dermoscopic image processing for the detection of skin lesions, most notably melanoma [29-33]. The potential for AI-assisted triage using tele-dermoscopy is profound and may allow for decreased costs and improved access to dermatologic care. However, some have noted concerns that the images used to develop or test algorithms is often not reported, and when present, may lack a diversity in patient population [33]. Further research is needed to clarify these issues before AI is integrated into the clinic.

There are several limitations to the present study. The number of survey and discussion participants was small, and composed of providers with various levels of dermoscopic training who were recruited from a single academic institution. Additionally, the number of lesions included was small, and selection bias of representative images may limit interpretation of the results. The study also utilized images from the VISN 7 tele-dermatology program, which serves a large number of fair skinned individuals. Skin lesions in skin of color were underrepresented and could pose a potential pitfall for providers. Future studies should explicitly test the utility of dermoscopy for triaging patients with darker skin. This dataset was also limited to dermatologists and dermatology residents, while primary care providers are increasingly engaged in the interpretation of dermoscopic images [34]. Nonetheless, our pilot data suggests that dermoscopy images should be considered in future tele-dermatology care models, even after the pandemic is over. We encourage future studies to investigate the utility of dermoscopy for tele-dermatology in other populations including those with larger proportions skin of color patients.

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Dermoscopic Photographs Impact Confidence and Management of Remotely Triaged Skin Lesions

Tova Rogers¹, Myles Randolph McCrary, Howa Yeung, Loren Krueger, Suephy C Chen
Survey

Clinical image displayed and participants asked to answer the following questions:

Diagnostic Category
1. Cannot determine based on clinical photograph
2. Benign neoplastic
3. Malignant neoplastic
4. Infectious
5. Inflammatory

Triage Decision
1. Cannot make a decision based on clinical photograph
2. Reassure
3. Topical or systemic therapy
4. Biopsy

Level of urgency in which action is required
1. Not urgent
2. Urgent
3. Emergent

Confidence in triage decision
1. <=10%
2. 20%
3. 30%
4. 40%
5. 50%
6. 60%
7. 70%
8. 80%
9. 90%
10. 100%

Dermoscopic image displayed and participants asked to answer the following questions:

Diagnostic Category
6. Cannot determine based on dermoscopic photographs
7. Benign neoplastic
8. Malignant neoplastic
9. Infectious
10. Inflammatory

Triage Decision
5. Cannot make a decision based on dermoscopic photograph
6. Reassure
7. Topical or systemic therapy
8. Biopsy

Level of urgency in which action is required
4. Not urgent
5. Urgent
6. Emergent

Confidence in triage decision
11. <=10%
12. 20%
13. 30%
14. 40%
15. 50%
16. 60%
17. 70%
18. 80%
19. 90%
20. 100%

Debriefing prompts

How confident are you in your abilities to triage patients using clinical photographs?

How confident are you in your abilities to triage patients using dermoscopic photographs?

Since the onset of the coronavirus pandemic, we have been faced with triaging patients by phone. Clinical photographs are often unavailable. Dermoscopic photographs are almost universally unavailable. Has this changed your opinions about triaging with clinical photographs? Has this changed your opinions about triaging with dermoscopic photographs?

Do you think dermatoscopes should be made more accessible to consumers and primary care providers?
Habits of Using Social Media and the Internet in Psoriasis Patients

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11 İstanbul Medipol University, Faculty of Medicine, Department of Dermatological and Venereal Diseases
12 Trakya University, Faculty of Medicine, Department of Dermatological and Venereal Diseases
13 Dicle University, Faculty of Medicine, Department of Dermatological and Venereal Diseases
14 Health Sciences University, Haydarpaşa Training and Research Hospital Faculty of Medicine, Department of Dermatological and Venereal Diseases
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Key words: psoriasis, social media, internet, habit


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Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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Introduction
Psoriasis is a chronic systemic inflammatory disease seen at a rate of 1-3% across the world [1]. Sufferers may experience itching, burning and pain sensation, and restrictions in social life, which reduce their quality of life [2]. Social media (SM) comprises internet-based communication tools that have entered people lives very quickly [3]. It is utilized for many different purposes, such as accessing educational tools and creating educational resources, creating campaigns to reach the public, and even inviting patients to participate in clinical trials or online surveys [3]. Today, access to information through technology tools has become extremely easy and fast. As in every subject, the internet has become almost the first source of reference for health problems.

Although there are a few studies related to the use of SM and the internet conducted with patients presenting to dermatology outpatient clinics, there is no research specifically focusing on psoriasis patients [4,5]. Psoriasis affects the quality of life of patients due to recurrent nature of the disease, long-term and sometimes laborious treatment processes, accompanying symptoms including pain, itching, and xerosis, and involvement of visible areas such as the face or intimate parts of the body such as the genitals [6]. This prompts patients to explore different treatment options, seek different physicians and hospitals, and reach other patients and various medical organizations. In this respect, the internet and SM provide patients with a wide range of sources and fast access to information.

Objectives
This study aimed to explore the habits of patients with psoriasis related to their use of SM and the internet to obtain information about their disease, methods they used, whether they followed programs concerning the disease available on media outlets, whether they read related brochures, and their recommendations to dermatologists and dermatological associations concerning the use of SM related to psoriasis.

Methods
Patients
The study included voluntary literate psoriasis patients over the age of 18 years and who were followed in the psoriasis-specialized outpatient clinics of 18 different dermatology departments located in seven regions of Turkey between January 1, 2020, and July 1, 2020. Each researcher had to enroll at least 75 patients in the study [7]. Although part of the study coincided with the pandemic period, dermatology outpatient clinics were actively working in hospitals due to the regulations of the health authority.

Procedure
This is a non-interventional, cross-sectional multicenter study. Approval for the study was obtained from the ethics committee of the university (ID 25.12.2019/0527). The survey questions were prepared by the researchers. Information on the patients clinical findings and the Psoriasis Area Severity Index (PASI) scores were noted by their physicians.
patients were asked to complete the survey (Supplementary Table 1) and the Dermatology Life Quality Index (DLQI) questionnaire without any time limitation [8,9].

Statistical Analysis

Data obtained were analyzed using SPSS IBM software package at the 95% confidence level, ie, 5% margin of error. Descriptive statistics concerning the survey results were given as frequencies and percentages. In continuous measurements showing a normal distribution, paired-group comparisons were undertaken with the independent-samples t-test while three groups were compared using analysis of variance (ANOVA). In cases where there was a significant difference in ANOVA, the groups that caused the significant difference were examined using the least significant difference test as a post-hoc method. In continuous measurements that did not show a normal distribution, two groups were compared using the Mann-Whitney U test and three-group comparisons were undertaken with the Kruskal-Wallis H test. The test statistics for the comparison of two or more groups were obtained using the chi-squared test.

Results

A total of 1,520 participants (709 women and 811 men) were included in the study and all of them agreed to participate. Of the participants, 51.40% stated that they used SM and the internet regularly, 21.90% sometimes used them, and 26.70% never used them. In addition, of the participants who stated that they used SM and the internet, 48.38% regularly and 32.14% sometimes made inquiries about psoriasis on these platforms while 19.48% did not consult online platforms for this purpose.

The use of SM and the internet for psoriasis was significantly higher in young people, those with university or higher education levels. Although there was no significant difference between smokers and non-smokers, the smoking pack years were significantly higher in SM users than non-SM users (11±23 pack years, 9±14 pack years; \( P = 0.027 \), respectively). Social media and internet use in psoriasis patients were found not significantly associated with gender, marital status, alcohol use, and monthly family income (Table 1).

The use of the internet and SM for psoriasis-related inquiries was higher in Marmara region where the education level and the rate of working population are high, as well as in Central Anatolia where the capital of Turkey is located.

Social media and internet use was significantly higher in those with higher DLQI and PASI scores, those with facial, scalp, hand, genital and inverse involvement, and those with arthralgia/arthritis. Nail involvement, family history of psoriasis, and disease duration were not found associated with SM and internet use (Table 2). There was no difference between psoriasis subtypes in terms of SM and internet usage.

SM tools used by the participants to investigate psoriasis are shown in Figure 1. Most participants (86%) reported using Google for this purpose. The participants most frequently (76%) sought information about the disease itself, followed by...

<table>
<thead>
<tr>
<th>Frequency of social media use</th>
<th>Yes</th>
<th>No</th>
<th>Sometimes</th>
<th>Overall</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>238</td>
<td>122</td>
<td>159</td>
<td>519</td>
<td>0.136</td>
</tr>
<tr>
<td>Male</td>
<td>274</td>
<td>165</td>
<td>155</td>
<td>594</td>
<td>0.534</td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>356</td>
<td>211</td>
<td>214</td>
<td>781</td>
<td>0.336</td>
</tr>
<tr>
<td>Single</td>
<td>144</td>
<td>67</td>
<td>86</td>
<td>297</td>
<td>0.267</td>
</tr>
<tr>
<td>Divorced</td>
<td>13</td>
<td>9</td>
<td>14</td>
<td>36</td>
<td>0.326</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>277</td>
<td>161</td>
<td>188</td>
<td>626</td>
<td>0.193</td>
</tr>
<tr>
<td>Smoker</td>
<td>236</td>
<td>126</td>
<td>123</td>
<td>485</td>
<td>0.437</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>473</td>
<td>253</td>
<td>290</td>
<td>1016</td>
<td>0.173</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>32</td>
<td>24</td>
<td>95</td>
<td>0.86</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>404</td>
<td>228</td>
<td>252</td>
<td>884</td>
<td>0.918</td>
</tr>
<tr>
<td>Regularly</td>
<td>13</td>
<td>6</td>
<td>5</td>
<td>24</td>
<td>0.22</td>
</tr>
<tr>
<td>Social drinker</td>
<td>96</td>
<td>53</td>
<td>56</td>
<td>205</td>
<td>0.184</td>
</tr>
<tr>
<td>Monthly income level*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300$ and below</td>
<td>96</td>
<td>69</td>
<td>67</td>
<td>232</td>
<td>0.208</td>
</tr>
<tr>
<td>300-650$</td>
<td>277</td>
<td>135</td>
<td>169</td>
<td>581</td>
<td>0.522</td>
</tr>
<tr>
<td>650-1,300$</td>
<td>110</td>
<td>70</td>
<td>64</td>
<td>244</td>
<td>0.219</td>
</tr>
<tr>
<td>above 1,300$</td>
<td>29</td>
<td>13</td>
<td>14</td>
<td>56</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Table 1 continues
Table 1. Social media and internet use according to demographic characteristics. (continued)

<table>
<thead>
<tr>
<th>Frequency of social media use</th>
<th>Yes</th>
<th>No</th>
<th>Sometimes</th>
<th>Overall</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literate**</td>
<td>2</td>
<td>11.1%</td>
<td>10</td>
<td>55.6%</td>
<td>6</td>
</tr>
<tr>
<td>Primary-middle school</td>
<td>156</td>
<td>43.8%</td>
<td>99</td>
<td>27.8%</td>
<td>101</td>
</tr>
<tr>
<td>High school-college</td>
<td>208</td>
<td>46.3%</td>
<td>102</td>
<td>22.7%</td>
<td>139</td>
</tr>
<tr>
<td>University</td>
<td>129</td>
<td>50.0%</td>
<td>66</td>
<td>25.6%</td>
<td>63</td>
</tr>
<tr>
<td>Post-graduate (Masters-PhD)</td>
<td>17</td>
<td>56.7%</td>
<td>9</td>
<td>30.0%</td>
<td>4</td>
</tr>
<tr>
<td><strong>Age, years, mean ± standard deviation</strong></td>
<td>39 ± 13</td>
<td>43 ± 15</td>
<td>40 ± 13</td>
<td>41 ± 14</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Calculated based on the exchange rate at the time of the study.
**Refers to participants that have no formal education but know how to read and write.

Table 2. Social media and the internet use according to disease involvement.

<table>
<thead>
<tr>
<th>Frequency of social media use</th>
<th>Yes</th>
<th>No</th>
<th>Sometimes</th>
<th>Overall</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Joint pain/involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>120</td>
<td>45.1%</td>
<td>55</td>
<td>20.7%</td>
<td>91</td>
</tr>
<tr>
<td>Arthritis</td>
<td>73</td>
<td>52.9%</td>
<td>27</td>
<td>19.6%</td>
<td>38</td>
</tr>
<tr>
<td>Absent</td>
<td>287</td>
<td>43.4%</td>
<td>197</td>
<td>29.8%</td>
<td>178</td>
</tr>
<tr>
<td><strong>Nail involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>310</td>
<td>47.9%</td>
<td>167</td>
<td>25.8%</td>
<td>170</td>
</tr>
<tr>
<td>Present</td>
<td>203</td>
<td>43.5%</td>
<td>120</td>
<td>25.7%</td>
<td>144</td>
</tr>
<tr>
<td><strong>Scalp involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>217</td>
<td>43.3%</td>
<td>148</td>
<td>29.5%</td>
<td>136</td>
</tr>
<tr>
<td>Present</td>
<td>296</td>
<td>48.3%</td>
<td>139</td>
<td>22.7%</td>
<td>178</td>
</tr>
<tr>
<td><strong>Facial involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>402</td>
<td>44.4%</td>
<td>244</td>
<td>26.9%</td>
<td>260</td>
</tr>
<tr>
<td>Present</td>
<td>111</td>
<td>53.4%</td>
<td>43</td>
<td>20.7%</td>
<td>54</td>
</tr>
<tr>
<td><strong>Hand involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>324</td>
<td>46.0%</td>
<td>196</td>
<td>27.8%</td>
<td>184</td>
</tr>
<tr>
<td>Present</td>
<td>189</td>
<td>46.1%</td>
<td>91</td>
<td>22.2%</td>
<td>130</td>
</tr>
<tr>
<td><strong>Genital involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>382</td>
<td>44.2%</td>
<td>246</td>
<td>28.4%</td>
<td>237</td>
</tr>
<tr>
<td>Present</td>
<td>131</td>
<td>52.6%</td>
<td>41</td>
<td>16.5%</td>
<td>77</td>
</tr>
<tr>
<td><strong>Inverse involvement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>375</td>
<td>43.5%</td>
<td>249</td>
<td>28.9%</td>
<td>239</td>
</tr>
<tr>
<td>Present</td>
<td>138</td>
<td>55.0%</td>
<td>38</td>
<td>15.1%</td>
<td>75</td>
</tr>
<tr>
<td><strong>PASI</strong></td>
<td>6.8 ± 9</td>
<td>5.7 ± 9</td>
<td>6.8 ± 9</td>
<td>6.5 ± 9</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>DLQI</strong></td>
<td>10.3 ± 8.7</td>
<td>6.6 ± 7.1</td>
<td>9.7 ± 8.4</td>
<td>9.1 ± 8.4</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>14 ± 10</td>
<td>15 ± 11</td>
<td>15 ± 11</td>
<td>14 ± 10</td>
<td>0.217</td>
</tr>
<tr>
<td><strong>Family history of psoriasis</strong></td>
<td>188</td>
<td>44.0%</td>
<td>111</td>
<td>26.0%</td>
<td>128</td>
</tr>
</tbody>
</table>

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

by medication and treatment options (62%), physicians (40%), and other patients posts (43%). Of the respondents, 9.9% were members of SM groups related to psoriasis, 3.1% were former members, and 87% stated that they had never joined such a group. The platforms used for patient groups were Facebook for 80.3% of the participants, Instagram for 21.4%, WhatsApp for 10.3%, Twitter for 2.6%, and other platforms for 12%. When asked about their views on what was discussed in these groups, 35.7% of the respondents reported that they read the posts if they caught their attention, 23.6% looked for further information on what was discussed, 20.7% just read the posts, 22.2% felt relieved to see others with similar problems, and 8.4% thought that a physician or product was advertised in these online groups. We determined that 78.7% of the participants did not ask their physician about the accuracy of information obtained from SM and the internet (Figure 2A). In case of contradiction between their findings in internet search and their physicians’
recommendations, 84.6% of the participants stated that they would trust their physicians (Figure 2B).

Of the participants, 19.4% stated that they used SM to try to contact dermatologists to ask questions about their disease. When online platforms were used for this purpose, 14.2% of the participants considered that physicians should answer patients’ questions, 13.6% stated that only physicians working in private hospitals should answer such questions, 32.8% thought that physicians should respond politely even if they were not obliged to answer, and 43.6% believed that physicians did not have to answer. The participants stated that they most frequently (66.7%) tried to contact physicians by personal or clinic phone (Figure 3A). Of those that tried to contact via SM, they mostly used Facebook (49.3%) (Figure 3B). When they reached physicians, they mostly asked questions about their treatment (41.4%) and disease (31.1%). Furthermore, 8.7% stated that they sent physicians photographs of their symptoms in order to ask for their advice, 12% asked for help to get hospital appointments, and the remainder asked for advice on other skin diseases or the health problems of relatives. The majority of the participants that tried to contact physicians on SM (77.9%) added that they did not receive a response, while most of those that obtained a response (61.8%) mentioned that they followed physicians’ recommendations, 21.2% sometimes followed these recommendations, and 17% did not do what was recommended. When the participants were asked whether they would trust a physician’s answer if they directed him/her a question accompanied by a photograph, 56.6% responded as no, 11.4% as yes, and 32% as yes but they would still visit a physician for an examination.
Of the participants, 36.9% did not like the television and radio programs on psoriasis, 29% considered that such programs only aimed to promote physicians or advertise products, 31.7% wanted to be given information, and 22.8% stated that it was a relief to see other psoriasis patients. While 52.5% of the participants did not follow such programs, 14.5% followed them regularly and 33% sometimes watched them. Most of the respondents (83.9%) reported that they did not apply what they saw on television, and 9.1% always and 7% sometimes tried them. In addition, the participants made further inquiries about what they saw on television by consulting the internet (27.4%), a physician (18.4%), a pharmacist (7%), and other patients (8.2%). Among these participants, 13.6% sought further information if what was presented on television appeared logical while 46.3% did not make any further inquiries. Only 0.2% of the respondents contacted the television or radio program to ask questions. Of the participants, 75.2% stated that they never asked their physicians about what they saw on television programs while 10.6% asked such questions implicitly and 14.2% openly.

When asked whether they had read a book/brochure about psoriasis, 5.8% of the participants stated that they had, 71.7% had not, and 22.5% were not aware of such publications. Furthermore, 62.7% of the respondents wanted seminars on psoriasis to be given by physicians and 30.3% by official institutions, and 21.9% stated that they would attend such events if they were free, 9% would be willing to pay a fee, and 19.3% were not interested. More than half the participants (56.5%) reported that hospitals or physicians did not give them educational brochures while 26.9% were provided such publications and read them, and 16.6% were presented such materials but did not read them.

Table 3 summarizes the participants responses concerning their recommendations for dermatologists and dermatological associations. The respondents most frequently (62.8%) wanted the public to be informed that psoriasis was not contagious. Secondly (62%), the patients wanted the dermatologists and the dermatology associations to prepare the publications and information shown in SM and the

Table 3. Recommendations of the participants to dermatologists and dermatological associations concerning the use of social media and internet related to psoriasis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society should be made aware that the disease is not contagious.</td>
<td>955</td>
<td>62.8%</td>
</tr>
<tr>
<td>These publications should be prepared by the authorities in this area.</td>
<td>942</td>
<td>62.0%</td>
</tr>
<tr>
<td>Sharing false information should not be allowed.</td>
<td>831</td>
<td>54.7%</td>
</tr>
<tr>
<td>Society should be made aware that treatment is available for the disease.</td>
<td>752</td>
<td>49.5%</td>
</tr>
<tr>
<td>Only dermatologists should discuss the disease.</td>
<td>670</td>
<td>44.1%</td>
</tr>
<tr>
<td>Seminars should be organized in places easily accessible to the public.</td>
<td>573</td>
<td>37.7%</td>
</tr>
<tr>
<td>Associations should file a criminal complaint if inaccurate information is present.</td>
<td>494</td>
<td>32.5%</td>
</tr>
<tr>
<td>Books-booklets should be prepared and distributed.</td>
<td>449</td>
<td>29.5%</td>
</tr>
<tr>
<td>More media programs should be made available to present introductory information about the disease.</td>
<td>402</td>
<td>26.4%</td>
</tr>
<tr>
<td>Patient schools should be organized in hospitals.</td>
<td>353</td>
<td>23.2%</td>
</tr>
<tr>
<td>More information should be shared on the internet.</td>
<td>302</td>
<td>19.9%</td>
</tr>
</tbody>
</table>

Total percentage exceeds 100 since the participants were allowed to choose more than one option
internet. They (54.7%) also did not want to see false information about psoriasis on SM and the internet.

Conclusions

Our study showed that 80.5% of the patients with psoriasis had the habit of regularly or sometimes using SM and the internet to seek information about their disease. This behavior was more common in young people, those with university or higher education levels, those with higher DLQI and PASI scores, those with facial, scalp, hand, genital and inverse involvement, and those with arthralgia/arthritis. The most commonly used search engine was Google (86%) and the most commonly used SM platform was Facebook (41%).

While it is known that globally, 4.5% of online inquiries was related to health in the 2000s, this rate has gradually increased, reaching 79% today [4,10,11]. Patients resort to SM and the internet to obtain information about their diseases and treatments, communicate with other patients and physicians, and look for organizations related to their diseases [12].

A previous study conducted in the United States of America (USA) reported that 80% of internet users consulted the internet to access information about at least one disease throughout their lifetimes [13]. However among the studies conducted for this purpose, especially those related to internet use on a disease basis have not yet become widespread, and research on the general use of the internet about diseases has only accelerated in the last few years. Our study is the first to investigate the internet and SM use of patients with psoriasis and includes data obtained from 1,520 patients participating from different regions of Turkey.

In a study conducted with 460 patients who presented to a general dermatology outpatient clinic, the rate of those consulting SM was found to be 80% [14]. In another study conducted with patients who presented to the dermatology outpatient clinic in Saudi Arabia, this rate was found to be 47% [4]. In a general surgery study, the rate of patients referring to online research before hernia surgery was reported to be 67% [15]. In our study, the rate of patients with psoriasis stated that they resorted to the internet or SM to obtain information about their disease. The difference in this rate seems to be due to our research focusing on a specific chronic disease. The rate of online medical inquiries is also reported to be higher among women, people with higher income, those with higher education levels, and those more affected by the disease [5,14-16]. Similarly, in our study, we observed that the use of SM and the internet for psoriasis was statistically significantly higher in young people and highly educated individuals. In dietetic studies, the use of SM was found to be higher in women and in young adults aged 18 to 35 years [17]. In the current study, there was no gender difference, but internet and SM users had a mean lower age and higher education level. This can be explained by the higher internet and SM usage among young adults and those with a higher education level [18]. Furthermore, the more people quality of life was, the more likely they would look for a solution to their disease. In addition, it has been shown that the involvement of the visible parts of the body such as the face and hands and intimate parts such as the genitals and skin folds, as well as the presence of accompanying painful conditions, including arthralgia/arthritis are more likely to have negative psychosocial effects on patients and result in higher DLQI scores [6]. Unsurprisingly, in the presence of such involvements, patients tend to make more online inquiries concerning their disease.

In the USA, the rate of individuals referring to Facebook to obtain information about health was found to be 38% [19]. In a study conducted with dermatology patients, it was shown that the patients obtained information about their physicians through SM 9.7 times more frequently compared to traditional media sources [11]. The source of this information was mostly Twitter (44.5%), followed by Instagram (27.9%), and Facebook (2.8%). However, the authors did not include search engines such as Google in their study [11]. In another study, the patients most frequently used Google (42.3%), followed by YouTube (34.6%) and Facebook (22.3%) for their medical searches [5]. In our study, 86% of the patients used Google for this purpose, while 41% used Facebook, 33% YouTube, 31% Instagram, and 8% Twitter. Since Google is globally the most used search engine as in our country, it is natural for patients to seek information about their diseases using this engine. Facebook is the most frequently used SM tool for adults using the internet [20]. However, SM habits can change over time. Some websites/applications may lose popularity while others may become more popular or their popularity may fluctuate. In addition, SM applications can be expected to vary according to geographical regions [21].

One of the interesting findings of our study is that 19% of the participants used patient blogs to obtain information. In addition, 22.8% stated that it was a relief seeing patients with psoriasis like themselves on traditional media programs such as television. In general, patients express that they feel comfortable and less embarrassed when they meet people with the same disease and exchange views about their disease [22]. The findings from our study indicate that patients are interested in what other patients with the same disease experience and they may even compare their experiences to others, and it is comforting for them to realize that there are others that suffer from the same problems.

Our participants reported that they mostly consulted the internet to seek information about their disease, followed by treatment options and physicians. Patients motivations to
resort to SM and the internet to obtain information about their diseases can be listed as understanding the disease, exploring personal diagnosis-treatment methods and alternative treatments, and obtaining information about doctors and hospitals. However, they still consider physicians as the most trustworthy source [14]. In our study, 84.6% of the participants stated that even if they conducted online searches, they would trust the physician in the presence of conflicting information. As a more interesting finding, 56.6% of the participants stated that even if they had been given the opportunity to obtain information about their disease by sending photographs to their physician, they would not have trusted the physician response and 32% would still go to a physician for an examination. This shows that although the patients trusted physicians’ knowledge, they would still prefer to be personally examined by a physician and exchange ideas.

In this study, 78.7% of the respondents stated that they did not share with their physicians what they inquired about on the internet related to their disease, which is in agreement with previous studies. This can be interpreted as patients not being willing to disclose to their physicians that they consult online sources and they may even be concerned about their physicians’ reaction.

When asked about their recommendations to dermatologists and dermatological associations regarding the use of SM, internet and traditional media, most of the participants (62.8%) stated that society should be informed that psoriasis is not contagious. In addition, they stated that informative publications and broadcasts should be prepared by the authorities in the field, such as dermatologists (62%) and that false information about the disease should not be allowed to spread (54.7%). It is now widely known that psoriasis is not contagious, but even today patients with lesions, especially in visible areas still express that other people refrain from touching them or shaking hands [23,24]. In this respect, it is very important that three out of every five participants in the current study recommended that the public should be informed about the non-contagious nature of the disease. It is clear that this situation affects the social relationships of patients.

The main limitations of our study are that the data were collected through a survey, and therefore they were based on the self-reported statements of the patients and a part of the study period coincided with the ongoing pandemic. During the first months of the pandemic, working from home may make the patients access SM frequently. A comparison with another chronic skin disease or with a control group may be done for further studies. However, this study is important due to being the first in this area, multicenter design involving the whole country, and inclusion of a large patient series.

Although SM comprises many favorable characteristics, such as allowing for the mutual exchange of information and comments, it is inevitable that some of the shared information is false. Our study showed that a high rate of patients with psoriasis consulted online sources to seek information about their disease. They most frequently used Google, Facebook, and YouTube channels to obtain information about the disease, treatment options, and doctors. However, although they consulted the internet and SM to seek information, most stated that they had greater trust in the information given by physicians. They also followed patient blogs and were relieved to see the presence of other patients suffering from psoriasis. They expressed their discomfort with the misbelief of a section of society without the disease that psoriasis is contagious, and they recommended dermatologists and dermatological associations to educate the public in this regard. As dermatologists, we have great responsibility in sharing accurate information about psoriasis on SM and the internet, as well as raising the awareness of society.

References


**Supplementary Table 1. Survey questions directed to the participants**

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you actively using social media and the internet?</td>
</tr>
<tr>
<td>Are you using social media and the internet to obtain information about psoriasis?</td>
</tr>
<tr>
<td>If yes, Which social media/internet platforms are you using?</td>
</tr>
<tr>
<td>What subjects are you inquiring about concerning your disease?</td>
</tr>
<tr>
<td>Are you a member of any online patient groups? If yes, which social media groups?</td>
</tr>
<tr>
<td>Are you following/writing posts in these groups? What do you think about these groups?</td>
</tr>
<tr>
<td>Would you share with your physician what you have seen on online about your disease?</td>
</tr>
<tr>
<td>If the information on social media conflicts what your physician says, which would you trust?</td>
</tr>
<tr>
<td>If you consult a dermatologist with a photograph of your disease on social media, would you trust his/her answer?</td>
</tr>
<tr>
<td>Are you trying to contact physicians using social media? If yes, on which platforms?</td>
</tr>
<tr>
<td>When you contact a physician online, do you think he/she is obliged to answer your questions about your disease?</td>
</tr>
<tr>
<td>What do you ask physicians that you contact online?</td>
</tr>
<tr>
<td>Do you trust their answers? Do you follow their recommendations?</td>
</tr>
<tr>
<td>What do you think about the health programs on television/radio concerning your disease?</td>
</tr>
<tr>
<td>Do you follow these programs? Do you further investigate what you see in these programs?</td>
</tr>
<tr>
<td>Would you consult your physician about the information presented in these programs?</td>
</tr>
<tr>
<td>Have you ever applied the recommendations you have seen in these programs to relieve your disease?</td>
</tr>
<tr>
<td>Do you read books/brochures on psoriasis? Do you read information booklets provided by physicians?</td>
</tr>
<tr>
<td>Would you like educational seminars to be organized on psoriasis?</td>
</tr>
<tr>
<td>Do you have any recommendations to dermatologists and dermatological associations concerning the use of social media/media related to psoriasis?</td>
</tr>
</tbody>
</table>
Dermoscopy in the Diagnostics of Incontinentia Pigmenti Skin Lesions

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Key words: Incontinentia pigmenti, skin stages, skin histopathology, Blaschko lines, dermoscopy

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ABSTRACT

Introduction: Incontinentia pigmenti (IP) is a rare X-linked geno-dermatosis characterized by numerous findings. Skin biopsy and histopathological analysis are considered as minor criteria for the diagnosis of IP. We assume that dermoscopy can assist the earlier diagnosis of IP.

Objectives: To gain experience in earlier diagnosis of IP by observing dermoscopic findings of cutaneous changes.

Methods: We revised confirmed cases of IP and examined them using dermoscopy, comparing histopathological and dermoscopic results.

Results: Stage I presented solitary and grouped vesicles in linear arrangement on erythematous skin. Early stage II presented star-shaped verrucous lesions on erythematous or pigmented skin. In well-developed lesions, dotted vessels surround keratotic part, some with thrombosed capillaries, resembling a viral wart. Stage III presented linear brown dots on the pigmented areas. Dermoscopic image was uniform in all the examined pigmented Blaschko linear changes. Stage IV presented numerous dotted vessels on the hypopigmented skin. Terminal hair was scarce or absent in all four stages. The surrounding normal skin had perifollicular depigmentations in stages III and IV.

Conclusions: Dermoscopy of all four stages is very specific compared to the dermoscopy of inflammatory dermatoses and pigmentations. Stage III has very close clinical, histological and dermoscopic mimickers and needs to be carefully examined with obligatory genetic testing. Dermoscopy of the stage IV closely corresponds to histopathological findings and may be crucial as a quick tool in revealing potential IP gene carriers. Dermoscopy should be used in addition to clinical examination since the two methods are complementary.
Introduction

Incontinentia pigmenti (IP; Bloch-Sulzberger syndrome) is a rare X-linked genetic disorder with an estimated prevalence of 1.2/100,000 [1,2]. It appears almost exclusively in females and is usually lethal in males [3]. It is caused by a mutation of the IKBKG gene localized on the X chromosome locus Xq28, which is the only gene known to be associated with IP [2]. The most prominent clinical manifestations of IP are considered to be skin changes, which constitute major IP diagnostic criteria [4,5]. Skin changes in IP occur along the lines of Blaschko throughout four stages: vesiculobullous (I), verrucous (II), hyperpigmented (III), and atrophic or hypopigmented (IV) [2,4].

Objectives

Beside clinical examination, skin biopsy and IKBKG gene analysis are the methods used in diagnosing IP. Since these methods are time consuming and invasive, we suggest that there is also a need for a faster and easier method as an adjunct to clinical diagnosis.

Methods

We clinically examined 2 female probands and one proband mother with signs of IP on the skin, which were confirmed by biopsy, and genetical examination – exons 4–10 deletion on the IKBKG gene. We have used a DermLite Hybrid M Dermatoscope (3 GEN) with immersion fluid and initial 10x magnification in a polarized mode coupled with a Nikon J3 camera (Nikon corporation). The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of University Clinical Center of Serbia (protocol code 251/4 and date of approval May 21, 2021). Informed consent was obtained from all subjects involved in the study.

Results

Case 1

The proband was 2 weeks old at the initial visit, phototype II, presented with vesiculobullous lesions grouped in stripe-like shapes following the lines of Blaschko (Figure 1A). Three months later, the proband had several verrucous changes (Figure 1B), hyperpigmented maculas, and very few vesicles. When six-months-old, there were Blaschko linear, slightly erythematous and pigmented changes forming atrophic lines with a verrucous part (Figure 1C). Biopsy was performed at the first and dermoscopy at all 3 clinical visits of the patient (Figure 1, D-H). In stage I we found solitary and grouped vesicles in a linear arrangement with yellowish content and serocrusts on an erythematous skin. Skin hair was significantly reduced on the affected area. In stage II, early verrucoid lesions are star-shaped, yellowish or whitish on an erythematous and a slightly pigmented skin. In well-developed lesions, dotted vessels surround a central keratinized part, or can be distributed on the lesion, with thrombosed capillaries, strikingly resembling a viral wart.

Case 2

The proband was one and a half months old at the initial visit, phototype IV, presented with hyperpigmented maculas following Blaschko lines as well as a few verrucous papules. Two biopsies were performed depicting stage II and III of IP (Figure 2, B and C). Clinical and dermoscopic examinations were performed at the age of 6 months, at stage III (Figure 2, A and D). As in previous stages, the affected area is devoid of terminal hair. We observed striking linear brown to gray-brown dots on the light brown pigmented areas. That dermoscopic image was uniform in all the examined pigmented Blaschko linear changes.

Case 3

The case 1 proband mother, phototype II, presented a slightly visible hypopigmented 6 cm macula on the lower extremity (Figure 3A). Anamnesis revealed a transitory skin eruption in childhood. The skin lesion was confirmed by biopsy as stage IV skin finding in IP (Figure 3B). Dermoscopy revealed numerous very small dotted vessels present on the surrounding hypo- and normally pigmented skin (Figure 3C). Terminal hair was very scarce or absent on the hypopigmented skin. The surrounding normal skin had perifollicular depigmentation.

Clinical summary data for all the patients are presented in Table 1.

Conclusions

Since some of the stages occur in utero, the diagnosis of IP may be delayed or overlooked. Clinical differential diagnosis should exclude other linear dermatoses along Blaschko lines: linear and whorled nevoid hypermelanosis (both familial and sporadic forms), hypomelanosis of Ito and lichen planus pigmentosus with Blaschkoid presentation [4,6-9].

By stages, the clinical differential diagnosis of IP in the stage I should exclude (ie congenital herpes simplex, varicella, bacterial infections, epidermolysis bullosa and bullous pemphigoid) [4,10,11]. In the stage II of IP, dermatologists should exclude verrucae vulgaris, X-linked-dominant chondrodysplasia punctata, linear verrucous epidermal nevus and lichen striatus [4,12]. Darier disease and prurigo nodularis
Figure 1. Case 1. (A) Blaschko lines distributed lesions (2-weeks-old). (B) verrucous formation on the middle digit (3-months-old). Verrucous lesions were present at the same time with scarce vesicles. (C) Blaschko linear, erythematous and pigmented atrophic line with a verrucous part (6-months-old). (D) Histology: spongiosis, vesicles with eosinophiles, and individual apoptotic keratinocytes in the epidermis. Lymphocytes and eosinophiles were present focally in the superficial dermis (H&E, x 20). (E) Dermoscopy: (magnification x10) Stage I, 2-weeks-old: new vesicles have yellowish center and erythematous halo (arrows), while the older lesions have yellowish serocrusts (star) surrounded by polycyclic scalling. The vesicle in the blue circle has been biopsied. (F) Stages I and II, 2-weeks-old: grouped vesicles with the yellowish content (0.5-2 mm in diameter) (star) and small verrucous lesion (star). (G) Stage II, 3-months-old (middle digit): well developed verrucoid lesion with scarce, tiny thrombosed dotted vessels (arrows) and slightly pigmented edge. Inset: star shaped early verrucous lesion. (H) Stage II-III, 6-months-old: verrucous lesion with thrombosed capillaries on an erythematous and slightly pigmented background. Atrophic part had shiny-white linear or polygonal streaks resembling chrysalis. Note: perifollicular depigmentation (black arrows).
Figure 2. Case 2. (A) Stage III, 6-months-old: pigmented Blaschko lines on the trunk and extremities (inset). (B) Stage II histology: compact hyperkeratosis, hyper-granulosis and prominent acanthosis with papillomatosis. Dyskeratotic cells were present in the epidermis as well as apoptotic like keratinocytes individually and in groups. Dilated blood vessels were visible in the dermal papillae, and lymphocytes and individual eosinophiles were present peri-vascularly. (H&E, x 20). (C) Stage III histology: individual cytoid bodies, and mild degree spongiosis focally in the epidermis. Proliferation of capillaries was visible in the papillary and superficial reticular dermis with eosinophiles as well as individual melanophages and free pigment. Homogenization of collagen was initiated focally in the papillary dermis (haematoxylin and eosin, x 20). (D) Stage III dermoscopy- linear gray- to gray-brown dots on the light brown pigmented background. The pigmentations were intermingled with normal skin and perifollicular depigmentation (stars).

Figure 3. Case 3. (A) Stage IV, 28-years-old: the only skin lesion was hypopigmented macule on the lower extremity. (B) Stage IV histology: mildly sparse melanocytes present focally in the atrophic epidermis, apoptotic bodies persisted. Absence of pilosebaceous units, eccrine glands and melanophages in the dermis. Homogenization of collagen was visible in the papillary dermis. Dilated capillary vessel(s) at the top of dermal papillae (H&E, x 20). (C) Stage IV dermoscopy (magnification 10x): perilesional and hypopigmented part had tiny dotted vessels, and scarce short linear vessels. Discrete, ill-defined white areas (stars) were observed. Inset: Note the perifollicular depigmentation of the hair in the surrounding skin.
may also be included. The stage III, as the hallmark stage of IP, one should distinguish from linear and whorled nev-oid hyper-melanosis and lichen planus pigmentosus with blaschkoid presentation [6,9,13]. The stage IV should be distin-guished from hypo-melanosis of Ito, vitiligo with local-ized alopecia, different types of ectodermal dysplasia, nevus anemicus, nevus depigmentosus, extragenital guttate lichen sclerosus, achromic pityriasis versicolor, idiopathic guttate hypomelanosis and postinflammatory hypopigmentations [4,13,14]. This stage may be difficult to detect in women with light skin, the most important reason why IP diagnosis is not made until adulthood in 52% of patients [15].

There have been only 2 cases of IP dermoscopy published so far: one with positive genetic findings, lacking a histology analysis, the other on dermoscopy on IP whorled alopecia and with no report on IKBKKG gene analysis [16,17].

Recently, the case of 13-month-old girl with linear and whorled hyperpigmentation preceded by vesicular lesions (anamnestic data) on the trunk and extremities at birth was published [18]. Genetic analysis was not performed, histology images were not provided. In our view, this was a typical case of blaschkoid lichen planus pigmmentosus, but not IP [19].

In dermoscopy of IP stage I, it was very easy to find a suit-able, small lesions for biopsy. They are clinically presented as seropapules and dermoscopically as yellowish seropapules with an erythematous halo. The main dermoscopic differential diagnosis is eczematous dermatitis and herpes simplex (Table 2) [20]. Tzanck smear searching for giant multinu-clear cells should be performed to eliminate the suspicion on neonatal herpes simplex [21]. Histological inflammation corre-sponds to dermoscopic erythema. Vesiculobullous formation was presented as either yellowish structures surrounded by an erythematous halo or grouped vesicles or serocrusts.

In dermoscopy of IP stage II, histologically, verrucous hyperplasia, compact hyperkeratosi, acanthosis and pap-ilomatosis correspond to the central verrucous part on dermoscopy are presented in table 2. Dilated blood vessels visible in the dermal papillae may correlate to the vessels changes dermoscopically observed. The reticular dermis is dense, fibrous and totally devoid of pilosebaceous units and sweat glands, and correlates with the absence of terminal hair observed on dermoscopy.

In dermoscopy of IP stage III, the main dermoscopic differential diagnosis is presented in Table 2. Linear brown to gray-brown dots are in accordance with previous 2 reports of IP dermoscopy of pigment stage [16,17]. Perifollicular depigmentation and disruptions in the normal reticular pigmentation of the surrounding skin have been observed. They have not been noted in any of the aforementioned conditions. Histopathological findings of this IP stage in our study also correspond to literature data and dermoscopy findings. Large deposits of free or intra-macrophagic melanin in the papillary dermis correspond to the gray-brown dots found on dermoscopy which is suggestive for pigment incontinence [9,15,22].

In dermoscopy of IP stage IV, the main dermoscopic differen-tial diagnosis is presented in Table 2. Histopathological findings of this IP stage correspond to our findings and literature data [15,23]. Homogenization of collagen in the papillary dermis corresponds to the white areas on the hypopigmented skin. Numerous dotted vessels seen on dermoscopy correspond to dilated capillary vessel(s) at the top of dermal papillae.

According to the presented findings and literature data, the greatest clinical, dermoscopic and histological mimics of IP are blaschkoid lichen planus pigmmentosus, and more loca-lized, blaschkoid lichen striatus [9,12,22]. Dermoscopically, the first condition has bluish-gray dots, globules, blotches and white lines or gray-brown dots arranged in a linear and reticular pattern [9,20]. The second condition has gray gran-ular pigmentations arranged in a linear manner and white lines [12]. Bluish gray pigmentations in both conditions cor-respond to melanin incontinence in the papillary dermis [9]. Furthermore, both conditions have apoptotic keratinocytes presented as colloid bodies and increased melanin and melan-ophages in the superficial dermis [9,12].

This report addresses all four IP skin stages, and follows up different consecutive IP stages presented in a single

---

**Table 1. Basic subject data when establishing Incontinentia pigmenti diagnosis and key laboratory and clinical findings**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at onset</th>
<th>Age of proband at 1st exam</th>
<th>IP stage at 1 exam</th>
<th>Skin stage(s) dermoscopy</th>
<th>Clinical findings</th>
<th>IKBKKG exon 4-10 deletion</th>
<th>Skin histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>At birth</td>
<td>2 weeks</td>
<td>I stage</td>
<td>I, II, III stage</td>
<td>Retinopathy praematuri</td>
<td>-</td>
<td>Stage I</td>
</tr>
<tr>
<td>Case 2</td>
<td>At birth</td>
<td>1.5 months</td>
<td>II, III stage</td>
<td>III stage</td>
<td>Retinopathy ishemica prolipherativa oculus sinister</td>
<td>Hypertonio discreta</td>
<td>Stage II and III</td>
</tr>
<tr>
<td>Case 3 (mother)</td>
<td>Unknown</td>
<td>28 years</td>
<td>IV stage</td>
<td>IV stage</td>
<td>-</td>
<td>-</td>
<td>+ Stage IV</td>
</tr>
</tbody>
</table>

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**Table 2. Differential diagnosis of the surrounding skin have been observed.**
patient. In all IP skin stages dermoscopic findings appear to be very characteristic and correlate to histopathological findings. Furthermore, dermoscopy can be used as an aid for determining the optimal lesion for diagnostic biopsy. Unlike the other stages, the stage III of IP has very close clinical, histological and dermoscopic mimickers and this stage needs to be carefully examined with obligatory genetic testing. The stage IV of IP in lighter phototypes is sometimes clinically barely visible, but has enormous clinical importance for diagnostics of potential IP gene carriers.

Further studies are needed to establish precise dermoscopic applicability in IP in the everyday practice of a dermatologist.

References


Evaluation of MCV/RDW Ratio and Correlations With Ferritin in Telogen Effluvium Patients

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Key words: Telogen effluvium, MCV/RDW, ferritin, correlation, alopecia

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ABSTRACT

Introduction: Telogen effluvium is one of the chronic diseases that affect the quality of life (QoL) in women. Genetic factors, vitamin deficiencies, hormonal and environmental conditions take roles in the etiology of hair loss.

Objectives: The study aimed to evaluate the RDW(Red cell distribution width)/MCV(Mean corpuscular volume) ratio and its correlation with ferritin in Telogen Effluvium patients and to reveal their potential role in the etiopathogenesis of Telogen effluvium.

Methods: We retrospectively evaluated the medical data of 250 patients who were admitted to the dermatology outpatient clinic between September 2020 and December 2020 with a diagnosis of telogen effluvium. The control group was created retrospectively from the medical records of 250 healthy individuals. HB(Hemoglobin), HCT(Hematocrit), MPV(mean platelet volume), MCV, RDW, ferritin, and MCV/RDW ratio of both groups were compared and evaluated statistically.

Results: All telogen effluvium patients were women in terms of gender. The mean age of the patient group was 33.11 ± 9.66 years and the mean age of the control group was 34.98 ± 12.37 years. The ratio of MCV/RDW, MPV, MCV, and ferritin is lower in the group with telogen effluvium compared to the control group and a statistically significant difference was found (P < 0.05).

Conclusions: Iron deficiency anemia is thought of as a factor in female patients with telogen effluvium. Although the data shows the correction of iron deficiency is insufficient telogen effluvium, we proposed that laboratory tests should be routinely used in the diagnosis and treatment phase of patients who apply with the complaint of hair loss.
Introduction

The etiology of hair loss consists of unavoidable genetic factors as well as hormonal reasons, vitamin deficiencies, and environmental reasons. Hair loss is seen as an important cosmetic problem that is increasing day by day, and therefore, the number of patients who apply to clinics is increasing [1,2].

Studies have shown that the most common cause of hair loss in women is telogen effluvium, and it's listed that the most common factors causing hair loss as low ferritin, vitamin B12 deficiency, and thyroid dysfunctions [3,4]. Iron deficiency is the most common nutritional deficiency in the world [5]. One of the many problems caused by iron deficiency is hair loss [3]. It can even be considered as one of the most accused factors in the etiology of this disease [6,7]. It is thought that hair loss develops due to the lack of iron, which plays a role in oxygen transport to the tissues, and the inability to carry enough oxygen to the hair follicle [8]. Iron is stored by ferritin together with apoferritin, and serum ferritin level reflects iron stores in the body [9]. Kantor et al found low serum iron levels in patients with diffuse hair loss in their study, while Rushton et al found low ferritin levels in 72% of the patients [10,11]. Özden et al reported that women with diffuse hair loss had a low ferritin value of 36%, and in another study when 72 mg of iron was given daily to 22 women with chronic hair loss, they have shown that hair loss decreased [5,12].

The red cell distribution range (RDW) is a measure of the heterogeneity of circulating erythrocytes. High RDW can generally occur as a result of increased erythrocyte destruction (hemolysis), nutritional deficiency, or blood transfusion [13]. In addition, RDW elevation is observed as a result of ineffective erythropoiesis due to chronic inflammation and neurohumoral activation [14].

Objectives

As far as we know, the role of iron, RDW, and MCV (Mean corpuscular volume) in hair loss seems unresolved so far. Since the laboratory reference intervals were different in the studies, the results were also controversial. The present study aimed to evaluate the RDW/MCV ratio and its correlation with ferritin in patients with telogen effluvium and to reveal the roles of telogen effluvium in its etiopathogenesis.

Methods

We retrospectively evaluated the medical data of 250 patients who were admitted to the dermatology outpatient clinic between September 2020 and December 2020 with a diagnosis of telogen effluvium. The diagnosis of telogen effluvium was performed as clinical. The control group was created retrospectively from medical records of 250 healthy individuals who applied to family health centers, with no complaints of hair loss or any other inflammatory skin disease, and were similar to the patient group in terms of mean age and gender. Patients who were in the period of chronic disease, stress, thyroid disease, pregnancy, lactation, had a history of surgical operation in the last 3 months, and took vitamin supplements were excluded from the study.

Serum ferritin levels were evaluated by electrochemiluminescence (ECLIA, Roche) method, and hemogram parameters (HGB, HCT, MPV, and RDW) were performed with Mindray BC-6800 (Mindray Bio-Medical Electronics Co., Ltd) hematology analyzer which analyzes complete blood count based on laser light scattering (forward and light scatter) and side fluorescent light. This retrospective study was approved by the Non-Invasive Clinical Research Ethics Committee of Necmettin Erbakan University (Decision No: 2021/3515). The study has conducted by the principles of the Declaration of Helsinki.

Statistical Analysis

SPSS version 25.0 program was used for database creation and statistical analysis. Pearson correlation test was used to measure the relationship and degree of relationship between variables and P < 0.05 was accepted as significance limit.

Results

All patients consisted of females in the study. The mean age of the patient group was 33.11 ± 9.66 years and the mean age of the control group was 34.98 ± 12.37 years. There was no difference between the two groups in terms of age (P > 0.05).

RDW value was elevated in telogen effluvium patients (P = 0.02), MPV and MCV values were decreased in telogen effluvium patients compared with the control group as P = 0.00 and P = 0.04, respectively. MCV/RDW ratio of the telogen effluvium patients was lower than the MCV/RDW ratio of the control group as 6.41 versus 7.41 (P = 0.00) (Table 1). The correlation between MCV/RDW ratio and ferritin was evaluated, and no significant correlation was found between the parameters (P > 0.05). When patients with telogen effluvium with positive and negative pull tests were compared, no statistically significant difference was found between the two groups in terms of HB, HCT, MPV, MCV, RDW, ferritin, and MCV/RDW ratios (P > 0.05) (Table 2).

Conclusions

Telogen effluvium is the most common cause of diffuse hair loss. Also, it's a non-cicatrical form of hair loss that develops approximately 3 months after a triggering factor and is characterized by widespread hair loss. Telogen effluvium
can be observed in both genders. On the other hand, women constitute the majority of patients who apply for treatment, because the frequency of the disease may be higher in women, or that the number of admissions in men is low and the cases remain subclinical [15,16].

Several studies were reported that fever, stress, major surgery, increase in androgen or estrogen hormone levels, hyperthyroidism, and many other causes have been associated with telogen effluvium [17]. To define the etiological diagnosis in telogen effluvium, a detailed history, and laboratory tests to exclude endocrine, nutritional, and autoimmune diseases should be performed [18].

While many studies have reported serum iron deficiency in telogen effluvium patients, some of them do not show a relationship between iron deficiency and the incidence of telogen effluvium [19]. Sinclair et al declared that low serum ferritin and hair loss were show not a relation between ferritin levels and hair loss [20]. A recent study reported that telogen effluvium patients had significantly lower serum ferritin concentrations compared to those in the control group (17.35 ± 18.54 ng/ml versus 39.27 ± 29.44 ng/ml, P = 0.001) [21]. As similar, patients with telogen effluvium had lower serum ferritin levels which compared to the control group in our study (28.83 µg/L versus 64.89 µg/L, P = 0.00) (Table 1).

Table 1. Comparison of some parameters between patient and control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>33.11±9.66</td>
<td>34.98±12.37</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>HB, g/dL</td>
<td>13.60</td>
<td>13.47</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>HCT, %</td>
<td>42.13</td>
<td>40.18</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>MPV, µm³</td>
<td>7.83</td>
<td>10.47</td>
<td>0.00</td>
</tr>
<tr>
<td>MCV, fl</td>
<td>84.22</td>
<td>86.65</td>
<td>0.04</td>
</tr>
<tr>
<td>RDW, %</td>
<td>14.30</td>
<td>11.68</td>
<td>0.02</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>28.83</td>
<td>64.89</td>
<td>0.00</td>
</tr>
<tr>
<td>MCV/RDW, fl/%</td>
<td>6.41</td>
<td>7.41</td>
<td>0.00</td>
</tr>
</tbody>
</table>

HB = hemoglobin; HCT = hematocrit; MPV = mean platelet volume; MCV = mean corpuscular volume; MCV/RDW m= mean corpuscular volume/red cell distribution width ratio; RDW = red cell distribution width; SD = standard deviation.

Table 2. Comparison of telogen effluvium with positive and negative pull test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pull test</th>
<th>N</th>
<th>Mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB</td>
<td>Positive</td>
<td>66</td>
<td>13.50</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>13.64</td>
<td></td>
</tr>
<tr>
<td>HCT</td>
<td>Positive</td>
<td>66</td>
<td>40.30</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>42.95</td>
<td></td>
</tr>
<tr>
<td>MPV</td>
<td>Positive</td>
<td>66</td>
<td>7.78</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>7.85</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>Positive</td>
<td>66</td>
<td>85.47</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>85.10</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td>Positive</td>
<td>66</td>
<td>11.72</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>11.66</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>Positive</td>
<td>66</td>
<td>30.71</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>27.97</td>
<td></td>
</tr>
<tr>
<td>MCV/RDW</td>
<td>Positive</td>
<td>66</td>
<td>7.43</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>146</td>
<td>7.41</td>
<td></td>
</tr>
</tbody>
</table>

HB = hemoglobin; HCT = hematocrit; MPV = mean platelet volume; MCV = mean corpuscular volume; MCV/RDW m= mean corpuscular volume/red cell distribution width ratio; RDW = red cell distribution width.
As a routine parameter, RDW represents the variation in diameters of red blood cells in the complete blood count [24]. RDW has been investigated in several diseases, such as rheumatoid arthritis, psoriasis, heart failure, and cutaneous vasculitis, and has been considered as a marker of inflammation [25]. The MCV/RDW ratio is used to evaluate for many diseases such as acute pancreatitis, cardiovascular disease [26,27]. While RDW value was elevated in telogen effluvium patients (P = 0.02), MPV and MCV values were decreased in telogen effluvium patients compared with the control group as P = 0.00 and P = 0.04, respectively. MCV/RDW ratio of telogen effluvium patients was lower than the MCV/RDW ratio control group as 6.41 versus 7.41 (P = 0.00). Also, the correlation between MCV/RDW ratio and ferritin was evaluated in telogen effluvium patients compared with the control group as P = 0.00 (P = 0.02), MPV and MCV values were decreased in telogen effluvium patients as 6.41 versus 7.41 (P = 0.00). Also, the correlation between MCV/RDW ratio and ferritin was evaluated in telogen effluvium patients, and no significant differences were found between the patient and control group (P > 0.05) (Table 2).

From the literature, controversial findings of related parameters were observed in Telogen effluvium. To clarify our study results, more comprehensive and further studies are needed.

References

Retrospective Analysis of Dermatological Diseases in Geriatric Patients During Dermatology Outpatient Department Visits

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ABSTRACT

Introduction: The elderly population is vulnerable to experience a great number of dermatological diseases thanks to the intrinsic and extrinsic process of aging.

Objectives: The aim of this study is to retrospectively investigate the prevalence of dermatological diseases in geriatric patients, their distribution by age and gender, and to provide a reference for studies on aging and skin problems.

Methods: In the present study, patients who reported to the dermatology outpatient clinic between January 1 2019, and January 1 2021, were evaluated retrospectively. As a result of examining the records of patients, 887 patients over the age of 65 who met the study protocol were included.

Results: The three most common diseases in all geriatric patients were fungal infections, eczematous dermatitis, and pruritus. Fungal infections were frequent in males and the 65-74 age group. In the males, the more frequent were precancerous lesions and malignant neoplasms, whereas in the females it was urticaria and adverse drug reactions. In the logistic regression model, the risk of fungal infection in geriatric patients was increased by being male (odds ratio 1.55, P = 0.006) and being in the range of 65-74 years old (odds ratio 1.46, P = 0.025). Male patients were at significantly higher risk for precancerous and malignant lesions (OR:2.81 P < 0.001) and actinic keratosis (odds ratio 3.26, P < 0.001) in this disease group.
**Introduction**

Due to technological advancements and improved living conditions/standards, life expectancy in Turkey as in other parts of the world is increasing on a daily basis. According to the Turkish Statistical Institute, life expectancy at birth increased from 78.0 for the 2013-2015 period to 78.6 for the 2017-2019 period. Similarly, life expectancy at age 65 for both sexes was 17.8 years in the 2013-2015 period, while it was 18 years in the 2017-2019 period [1]. In the last five years, the proportion of the elderly population, which includes individuals aged 65 and over, increased from 8.2% to 9.5%. It is estimated that the proportion of the elderly population will increase to 11% in 2025, 12.9% in 2030, and 16.3% in 2040 [2].

The geriatric population consists of individuals aged 65 and over. Aging is a continuous biological process. During the aging process, many functions such as regeneration capacity, chemical cleaning capacity, DNA repair capacity, sensory perception, mechanical protection and immune response of cells forming organs, and tissues decline. Due to the effect of these changing cellular functions, the skin structure is adversely affected as in all other organs and systems. The effects of aging on the skin are evaluated under two different pathways as intrinsic and extrinsic pathways. Intrinsic aging is considered the unavoidable and unstoppable physiological regression of the functions of cells and tissues. Extrinsic aging on the other hand, is both preventable and avoidable. It occurs as a result of exposure to environmental influences such as sunlight and ultraviolet radiation. The effects of extrinsic aging on the skin include not only physiological but also morphological changes. As a result of these aging mechanisms, there is dryness, wrinkles, flabbiness, and loss of flexibility of the skin and many benign neoplasms also occur in the skin due to aging [3].

**Objectives**

Due to the physiological and morphological effects of aging on the skin and the increase in the number of the elderly in the population over time, dermatological diseases associated with aging have become an important field of study. The aim of this study is to retrospectively investigate the prevalence of dermatological diseases in geriatric patients, their distribution by age and gender, and to provide a reference for studies on aging and skin problems.

**Methods**

In this study, patients who reported to the dermatology outpatient clinic between January 1, 2019, and January 1, 2021, were evaluated retrospectively. The records of 887 patients over the age of 65 were examined; 485 (54.7%) of them were females and 402 (45.3%) of them were males.

The participants were grouped by gender and by age groups of 65-74 years and 75 years or older. According to the diagnoses, skin diseases and disorders were categorized into 12 groups: viral infections, bacterial infections, fungal infections, eczematous dermatitis, papulosquamous diseases, vesiculobullous diseases, precancerous lesions and malignant neoplasms, benign neoplasms, xerosis cutis, pruritus, urticaria and adverse drug reactions and other diseases (cutaneous lymphomas, pigmentation disorders, connective tissue diseases, vascular diseases, metabolic skin diseases, acne and related diseases, hair disorders, nail disorders, skin ulcers).

Data analysis was performed using SPSS 23.0 statistical program. Descriptive statistical parameters were used for the prevalence of skin diseases. Chi-square analysis was used to determine whether there was a significant difference in the prevalence of skin diseases according to gender and age group. A logistic regression model was established for each of the diseases that were significant in the chi-square analysis. A value of \( P < 0.05 \) was accepted as significant in the entire analysis. Ethics committee approval was obtained from the university ethics committee.

**Results**

All the 887 patients whose records were examined were geriatric patients aged 65 and over. Of these patients, 485 (54.7%) were females and 402 (45.3%) were males. The mean age was 73.34 ± 7.24 (65-101) for women, 73.75 ± 7.08 (65-94) for men, and 73.53 ± 7.16 (65-101) years for all participants. Five hundred and thirty-nine (60.8%) of the participants were in the age group of 65-74 years and 348 (39.2%) were in the age group of 75 years and over. Of the individuals in the 65-74 age group, 304 (56.4%) were females and 235 (43.6%) were males. One hundred and eighty-one (52.0%) of the individuals in the 75 years and over age group were females and 167 (48%) were males.

Diseases seen during the entire study period are recorded as: fungal infections (23.0%), eczematous dermatitis (17.1%), pruritus (10.8%), papulosquamous diseases
(8.1%), viral infections (7.8%), precancerous lesions and malignant neoplasms (7.2%), benign neoplasms (5.3%), xerosis cutis (4.7%), urticaria and adverse drug reactions (3.2%), bacterial infections (2.5%), vesiculobullous diseases (0.9%) and other diseases (9.1%) (Tables 1 and 2).

Fungal infections were most common in men and women between the ages of 65 and 74, and the incidence in this age range was between 72.6% and 62.4%. Fungal infections in both sexes; tinea ungium (63.7%), tinea pedis (23.5%), tinea cruris (5.9%), tinea corporis (5.4%) and candida stomatitis (1.5%).

Eczematous dermatitis, which is the second most common dermatologic disease in the geriatric population, was most common in men and women between the ages of 65 and 74, with a prevalence of 64.4% and 54.8% in this age range. Eczematous dermatitis was seen in both sexes; allergic contact dermatitis (27.0%), irritant contact dermatitis (9.9%), nummular dermatitis (6.6%), lichen simplex chronicus (6.6%), and erythema intertrigo (3.9%).

Table 1. Distribution of diagnosed skin diseases by gender and results of chi-square analysis

<table>
<thead>
<tr>
<th>Dermatologic Diseases</th>
<th>Females N = 495 (%)</th>
<th>Males N = 402 (%)</th>
<th>Total N = 887 (%)</th>
<th>P value</th>
<th>X²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections</td>
<td>95 (19.6)</td>
<td>109 (27.1)</td>
<td>204 (23.0)</td>
<td>0.008</td>
<td>7.032</td>
</tr>
<tr>
<td>Eczematous dermatitis</td>
<td>90 (18.6)</td>
<td>62 (15.4)</td>
<td>152 (17.1)</td>
<td>0.218</td>
<td>1.520</td>
</tr>
<tr>
<td>Pruritus</td>
<td>52 (10.7)</td>
<td>44 (10.9)</td>
<td>96 (10.8)</td>
<td>0.915</td>
<td>0.011</td>
</tr>
<tr>
<td>Papulosquamous diseases</td>
<td>38 (7.8)</td>
<td>34 (8.5)</td>
<td>72 (8.1)</td>
<td>0.735</td>
<td>0.114</td>
</tr>
<tr>
<td>Viral infections</td>
<td>40 (8.2)</td>
<td>29 (7.2)</td>
<td>69 (7.8)</td>
<td>0.567</td>
<td>0.327</td>
</tr>
<tr>
<td>Precancerous lesions and malignant neoplasms</td>
<td>20 (4.1)</td>
<td>44 (10.9)</td>
<td>64 (7.2)</td>
<td>&lt; 0.001</td>
<td>15.278</td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>26 (5.4)</td>
<td>21 (5.2)</td>
<td>47 (5.3)</td>
<td>0.928</td>
<td>0.008</td>
</tr>
<tr>
<td>Xerosis cutis</td>
<td>28 (5.8)</td>
<td>14 (3.5)</td>
<td>42 (4.7)</td>
<td>0.110</td>
<td>2.557</td>
</tr>
<tr>
<td>Urticaria and Adverse drug reactions</td>
<td>24 (4.9)</td>
<td>4 (1.0)</td>
<td>28 (3.2)</td>
<td>0.001</td>
<td>11.238</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>11 (2.3)</td>
<td>11 (2.7)</td>
<td>22 (2.5)</td>
<td>0.655</td>
<td>0.199</td>
</tr>
<tr>
<td>Vesiculobullous diseases</td>
<td>5 (1.0)</td>
<td>3 (0.7)</td>
<td>8 (0.9)</td>
<td>0.655</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Table 2. Distribution of diagnosed skin diseases by age groups and results of chi-square analysis

<table>
<thead>
<tr>
<th>Dermatologic Diseases</th>
<th>65-74 years N = 539 (%)</th>
<th>75 years and over N = 348 (%)</th>
<th>Total N = 887 (%)</th>
<th>P value</th>
<th>X²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infections</td>
<td>137 (25.4)</td>
<td>67 (19.3)</td>
<td>204 (23.0)</td>
<td>0.033</td>
<td>4.538</td>
</tr>
<tr>
<td>Eczematous dermatitis</td>
<td>92 (17.1)</td>
<td>60 (17.2)</td>
<td>152 (17.1)</td>
<td>0.947</td>
<td>0.004</td>
</tr>
<tr>
<td>Pruritus</td>
<td>53 (9.8)</td>
<td>43 (12.4)</td>
<td>96 (10.8)</td>
<td>0.238</td>
<td>1.395</td>
</tr>
<tr>
<td>Papulosquamous diseases</td>
<td>41 (7.6)</td>
<td>31 (8.9)</td>
<td>72 (8.1)</td>
<td>0.488</td>
<td>0.480</td>
</tr>
<tr>
<td>Viral infections</td>
<td>39 (7.2)</td>
<td>30 (8.6)</td>
<td>69 (7.8)</td>
<td>0.452</td>
<td>0.565</td>
</tr>
<tr>
<td>Precancerous lesions and malignant neoplasms</td>
<td>33 (6.1)</td>
<td>31 (8.9)</td>
<td>64 (7.2)</td>
<td>0.117</td>
<td>2.451</td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>34 (6.3)</td>
<td>13 (3.7)</td>
<td>47 (5.3)</td>
<td>0.095</td>
<td>2.789</td>
</tr>
<tr>
<td>Xerosis cutis</td>
<td>20 (3.7)</td>
<td>22 (6.3)</td>
<td>42 (4.7)</td>
<td>0.074</td>
<td>3.197</td>
</tr>
<tr>
<td>Urticaria and Adverse drug reactions</td>
<td>20 (3.7)</td>
<td>8 (2.3)</td>
<td>28 (3.2)</td>
<td>0.240</td>
<td>1.379</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>11 (2.0)</td>
<td>11 (3.2)</td>
<td>22 (2.5)</td>
<td>0.295</td>
<td>1.097</td>
</tr>
<tr>
<td>Vesiculobullous diseases</td>
<td>4 (0.7)</td>
<td>4 (1.1)</td>
<td>8 (0.9)</td>
<td>0.531</td>
<td>0.393</td>
</tr>
</tbody>
</table>
Precancerous and malignant lesions were most common in women (55%) aged 75 years and above, while in men (54.5%) they were most common in the group of 65-74 years. Precancerous and malignant neoplasms seen in both sexes; actinoid keratosis (78.1%), squamous cell carcinoma (10.9%), mycosis fungoides (6.3%), basal cell carcinoma (3.1%), and lentigo maligna (1.6%).

Benign neoplasms were most common in women (69.2%) and men (76.2%) in the 65-74 years age group. Benign neoplasms were seen in both sexes; seborrheic keratosis (27.7%), skin tag (23.4%), epidermal cyst (14.9%), melanocytic nevus (14.9%) and keloid scar (4.3%). When the prevalence of skin diseases was analyzed by gender; fungal infections (p=0.008) and precancerous and malignant neoplasms (P < 0.001) were more common in males than females. Among the precancerous and malignant neoplasms, actinic keratosis (P < 0.001) was more common in males than females. When skin diseases were considered according to the distribution among age groups; Fungal infections were seen more frequently in the 65-74 age group (P = 0.033, significant) compared to the other age group. Tinea corporis (P = 0.039, significant) among fungal infections and allergic contact dermatitis among eczematous dermatitis (P = 0.046, significant) were seen more frequently in the 65-74 age group compared to the other age group (Tables 1 and 2).

A logistic regression model was established to analyze the extent to which the parameters with significant differences in the chi-square test increased the risk of developing skin diseases. According to the established logistic regression model, the risk of fungal infection in geriatric patients was increased by being male (odds ratio [OR] 1.55, P = 0.006) and being in the range of 65-74 years old (OR 1.46, P = 0.025). Male patients were at significantly higher risk for precancerous and malignant lesions (OR 2.81, P < 0.001) and actinic keratosis in this disease group (OR 3.26, P < 0.001) (Table 3).

Conclusions

While the average life expectancy in the world increases on one hand, on the other hand, efforts to take preventive measures on the health problems of geriatric patients, provide early diagnosis and necessary medical treatment not only improve their living conditions, but also reduce costs for countries [4,5]. According to 2020 data, 9.5% of Turkey’s population consists of individuals aged 65 and over [6]. In our study, 15% of the total number of patients who reported to the outpatient clinic were over 65 years old.

In this study, fungal infections, eczematous dermatitis, pruritus, papulosquamous diseases, and viral infections in order of the most prevalent to the least, constitute the first five most common dermatological diseases groups in the geriatric population. Bilgili et al. In a study conducted in an Eastern city in Turkey where winter conditions are severe, it is stated that in order of prevalence, the most common dermatological diseases are eczematous dermatitis, fungal infections, pruritus, urticaria-angioedema and bacterial infections. It is stated that viral infections and papulosquamous diseases are seen less frequently [7]. In another study conducted in Turkey, eczematous dermatitis, pruritus, fungal infections, precancerous and malignant lesions, and bacterial infections are listed as the most common dermatological diseases [8]. When we look at the studies conducted in Turkey related to the subject of the study, it is seen that the order of the most common dermatological disease groups changes according to geographical and climatic differences, but it is seen that eczematous dermatitis, fungal infections, pruritus disease group generally ranks high in the studies and maintains its significance.

In this study, fungal infections constitute the most common disease group in the geriatric population. In addition, fungal infections were 1.55 times more common in men and 1.46 times more common in the 65-74 age group. Similarly, in a study conducted by Yalçın et al in Turkey, fungal infections were reported to be more common in males (18%) and in the 65-74 years age group (16.7%) [9]. Age, gender, personal care, epidermal turn-over and decreased immunological functions may be responsible in the frequent occurrence of fungal infections in the geriatric population [10]. It is widely accepted that the fact that men are exposed to physical causal factors more than women and that they do not consider skin care as important as women, results in fungal infections being more common in men. This may be the reason why the prevalence of this disease was higher in males in our study too [9].

In this study, eczematous dermatitis constituted the second most common disease group in the geriatric population.

Table 3. Logistic regression model established for the estimation of risk factors leading to skin diseases

<table>
<thead>
<tr>
<th>Dermatologic Diseases</th>
<th>Risk Factor</th>
<th>B</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal infection</td>
<td>Male</td>
<td>0.442</td>
<td>&lt; 0.001</td>
<td>1.55</td>
<td>1.134 - 2.132</td>
</tr>
<tr>
<td></td>
<td>65-74 years</td>
<td>0.380</td>
<td>0.025</td>
<td>1.462</td>
<td>1.050 - 2.036</td>
</tr>
<tr>
<td>Precancerous and malignant lesion</td>
<td>Male</td>
<td>1.036</td>
<td>&lt; 0.001</td>
<td>2.819</td>
<td>1.631 - 4.871</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>Male</td>
<td>1.184</td>
<td>&lt; 0.001</td>
<td>3.267</td>
<td>1.735 - 6.152</td>
</tr>
</tbody>
</table>
Eczematous dermatitis is more common in the 65-74 years age group in both men and women. In addition, among eczematous dermatitis, contact dermatitis is the most common disorder. Similarly, in the study conducted by Yaldız et al, it is stated that allergic contact dermatitis (44.5%) and irritant contact dermatitis (33.2%) are the most common diseases among eczematous dermatitis [4]. The fact that eczematous dermatitis is more common in early geriatric ages and contact dermatitis is more common than others can be explained by the increased exposure to many environmental and physical extrinsic factors in the development of eczematous dermatitis. It is thought that it will continue to be seen more frequently in the coming years due to the changing climatic conditions, increasing exposure to sunlight and increasing chemical exposure.

In this study, pruritus was the third most common dermatological disease. Although it is seen at the same rate in women and men, it is of significance that it is seen at a higher rate in the 75 and over age group. Similarly, in a study conducted in Turkey, pruritus (12.8%) was the third most common disease and it was seen to increase from a rate of 12.2% in the 65-74 age group, to 14.3% in the 75-84 age group, and 16.9% in the 85 and over age group [11]. In a study conducted with 46 people staying in a nursing home in Denmark, the pruritus rate was reported as 28.9% [12]. It is acknowledged that the incidence of pruritus increases with age. Dry skin, nervous degeneration and weakening of immunity due to aging predispose the aged to pruritus [13]. Among the causes of diseases such as pruritus, it is important to have preventable or intervening measures in order to reduce this very common disease in later ages. For this reason, it can be said that patient information activities to be carried out in dermatology outpatient clinics and the study of preventive medicine by health professionals will be beneficial in reducing these diseases.

In this study, papulosquamous diseases was the fourth most common dermatological disease group. In this group of diseases, psoriasis vulgaris, seborrheic dermatitis and lichen planus, in order of prevalence, are the three most common diseases. In a study by Darjani et al in Iran, it was reported that papulosquamous patients were seen in 31.6% of geriatric patients, and seborrheic dermatitis (15.4%) and psoriasis (7.3%) were the first two in this group [14]. In a study conducted by Kandwal et al in India, it was reported that papulosquamous diseases (40%) and psoriasis (9.4%) as a constituent of this group were most common in individuals over 60 years of age [15].

In this study, precancerous and malignant lesions were seen in 7.2% of the geriatric population. Similar to our study, the prevalence of precancerous and malignant lesions was reported as 5.2% by Yalçın et al, 9.6% by Polat et al, and 9.7% by Yaldız et al [4,8,9]. Among these lesions, actinic keratosis, squamous cell carcinoma and mycosis fungoides in decreasing order of prevalence constitute the three most common lesions. When evaluated as a group, these lesions are 2.81 times more frequent in male subjects compared to female subjects. In this study, the prevalence of actinic keratosis was 5.6%. In addition, the risk of developing actinic keratosis, which is a common premalignant lesion, is 3.26 times higher in men. Prevalence of actinic keratosis has been reported as 29.3% by Kılıç et al, 22.3% by Cvitanovic et al, and 21.1% by Akdeniz et al [16-18]. Likewise, in the study of Akdeniz et al, it was emphasized that actinic keratosis was significantly more common in men [18]. Actinic keratosis usually presents as red or brown papules 3-6 mm in diameter on sun-exposed body parts in fair-skinned individuals [19]. The fact that men are exposed to sunlight more frequently in working and social life is acknowledged as one of the important factors that cause it to be more common in men.

The average life expectancy in most of the world is getting to continue increases due to preventive approaches and improving treatment options. As depend on this condition, geriatric patients take part in the focus of given medical services higher. An important part of the skin problems seen in geriatric patients are diseases that can be prevented by protecting individuals against adverse environmental conditions. These diseases cause life-threatening conditions albeit at a low rate. It is very important to determine the risk levels of individuals in the geriatric population for dermatological diseases that adversely affect the quality of life. It can supply to improve the medical services given by dermatologists to geriatrics. We believe that this epidemiological study will contribute to the dermatologists and clinicians in assessment and improving preventive approaches to the most seen skin diseases in geriatric.

References


**Introduction:** Dermoscopy is a noninvasive and easy to apply technique that allows in vivo magnification of the skin and thus observation of morphologic structures invisible to the naked eye. Recently, it gained popularity for evaluation of inflammatory skin conditions. In the field of connective tissue diseases, dermoscopy has been used mainly as a simple and accessible substitute of nailfold capillaroscopy.

**Objectives:** The aim of the present study is to expand the application of dermoscopy in patients with dermatomyositis (DM) beyond the usual nailfold examination. A clinico-dermoscopic correlation between clinical signs of skin affection and dermoscopic features is also suggested.

**Methods:** A total of 29 patients with DM were enrolled in this descriptive prospective study, conducted over a 3-year period. Dermoscopy was performed by a DermLite DL1 dermatoscope on polarization mode, attached to One Plus 3T camera. The following skin lesions were examined: periungual affection, scalp DM, Gottron papules, palmar papules, poikiloderma and auricular changes.

**Results:** Dermoscopy detected predominantly advanced nail fold capillary changes - giant capillaries (79%), microhemorrhages (46%) and avascular areas (25%). The most prevalent trichoscopic features were enlarged tortuous capillaries (64%), interfollicular scales (50%) and peripilar casts and tufting (36%). Among the other skin lesions assessed in this study - Gottron papules were present in 20 patients, poikiloderma in 11, palmar papules in 4 and auricular lesions in 4 patients.

**Conclusions:** The use of dermoscopy for clinical evaluation of skin lesions in DM enhances diagnostic accuracy and elucidates poorly known characteristics of the disease.
Introduction

Dermoscopy (epiluminescence microscopy) is a noninvasive and easy to apply technique that allows in vivo magnification of the skin and observation of morphologic features invisible to the naked eye. In the last decades dermoscopy has become a key tool for the evaluation of pigmented and nonpigmented skin tumors. Recently, an increasing number of publications have appeared that demonstrate the role of the handheld dermatoscope in an entirely new field - the field of inflammatory skin lesions. A huge break-through in this direction was the expert consensus published in 2020 on behalf of the International Dermoscopy Society providing a set of standardized basic dermoscopic parameters to follow when evaluating inflammatory, infiltrative and infectious dermatoses [1].

Nailfold capillaroscopy (NFC) is currently considered the gold standard for early assessment of microvascular changes in the nailfold area of patients with rheumatic diseases. As a simpler and more accessible method than NFC, dermoscopy has also been tested for gross analysis of capillary nailfold abnormalities in several studies comprising patients with collagen-vascular disorders [2,3].

Dermatomyositis (DM) is a rare autoimmune connective tissue disease that affects the skin, the skeletal muscles and the internal organs. Although its pathogenesis is not fully understood, the immune response is thought to originate from the capillary endothelium of the endomysium. An activation of the complement pathway and deposition of C5b-9 membrane attack complexes results in depletion of capillaries, ischemia, muscle and skin injury [4]. Therefore, vascular skin changes are fundamental for DM and a variety of vascular patterns might be observed via dermoscopy.

Objectives

The aim of the present study is to expand the application of dermoscopy in patients with DM beyond the simple nailfold examination. In order to do that, we have performed dermoscopy of other skin lesions, such as scalp DM, Gottron papules, palmar papules, poikiloderma and auricular lesions in the quest for subtle diagnostic clues, invisible to the unaided eye. In addition, we suggest a clinico-dermoscopic correlation be quest for subtle diagnostic clues, invisible to the unaided eye. In order to do that, we have performed dermoscopy of other skin lesions, such as scalp DM, Gottron papules, palmar papules, poikiloderma and auricular lesions in the quest for subtle diagnostic clues, invisible to the unaided eye. In addition, we suggest a clinico-dermoscopic correlation be

Methods

Twenty-nine patients with classic DM (CDM, 22 patients), clinically amyopathic DM (CADM, 4 patients) and DM/overlap syndrome with another connective tissue disease (3 patients), such as systemic lupus erythematosus and systemic sclerosis were enrolled in this prospective descriptive study. The study was conducted in the Department of Dermatology and Venereology, Alexandrovskia University Hospital, Sofia, Bulgaria between September 2018 and August 2021. Only patients with diagnosis of definite DM according to Bohan and Peter criteria for classic DM were included [5]. Patients with amyopathic DM were selected based on clinical skin findings, suggested by Sontheimer [6,7]. Additional examinations comprised serum enzyme levels, myositis-specific autoantibodies, electromyography, and skin biopsy. The mean age was 51 years (range: 19-77 years). Twenty patients were females (69%) and 9 patients were males (31%). A cancer-associated, or paraneoplastic DM was diagnosed in 10 patients (breast carcinoma in 2 patients, cervical carcinoma in 2, thyroid carcinoma in one, endometrial carcinoma in 2, ovarian carcinoma in one, cecal carcinoma in one, and bladder carcinoma in one). The disease duration ranged between 1 month and 23 years, and 69% of the patients had a maximal disease duration of 3 years. All the 29 patients were included in the study after signing a written informed consent.

The dermoscopic examination was performed by a DermLite DL1 dermatoscope on polarization mode, attached to One Plus 3T camera.

Results

Affection of periungual skin was assessed by the following clinical parameters-ragged cuticles, erythema, nail fold telangiectasias visible by naked eye, erosions/ulcerations, skin atrophy. Ragged cuticles (N = 14,58%) and nail fold erythema (N = 14,58%) were relatively common in our patients. Some patients had only one of these parameters, and some of them had both. Macroscopic nail fold telangiectasias (N = 1), erosions/ulcerations (N = 2) and skin atrophy of the periungual area (N = 1) were a rare finding (supplementary Table S1; Figure 1).

Specific dermoscopic features were divided into 5 groups - subtle changes or disorganization of the normal capillary architecture, enlarged/giant capillaries, microhemorrhages (defined by > 2 microhemorrhages per digit or confluent hemorrhagic zones), loss of capillaries/large avascular areas, and ramifications/bushy capillaries. Most of the patients had more pronounced nail fold capillary changes therefore only three patients presented with disorganization of the normal capillary architecture (13%). Enlarged/giant capillaries were the most common dermoscopic feature and occurred in nineteen patients (79%). Other signs like microhemorrhages, avascular areas and bushy capillaries were found in 46% (N = 11), 25% (N = 6) and 13% (N = 3) of the patients respectively (supplementary Table S1; Figure 11).
Clinical signs of scalp affection comprised erythema (N = 12, 55%), scaling (N = 11, 50%), non-scarring alopecia (N = 14, 64%), as well as calcinosis cutis and erosions/ulcerations (none of the patients). Pruritus was reported by 16 patients (73%).

Dermoscopy of the scalp, also called trichoscopy, revealed enlarged tortuous capillaries in fourteen patients (64%), peripilar casts and tufting in eight patients (36%), interfollicular scales in eleven patients (50%), bushy capillaries in three patients (14%), interfollicular pigmentation in five patients (23%), perifollicular pigmentation in two patients (9%), vascular lake-like structures in seven patients (32%), punctuate hemorrhages in one patient (5%). Hair shaft abnormalities were also detected - broken hairs (n=2; 9%), pigtail hairs (n=1; 5%), in the absence of other conditions, that may present with such hair defects (e.g., fungal infection, alopecia areata etc.). Clinical and dermoscopic parameters concerning scalp affection are shown on supplementary Table S1 and Figure 2.

Dermoscopy of Gottron papules visualized erythema (N = 20, 100%), scaling (N = 20, 100%), skin atrophy (N = 1, 5%), irregularly arranged vessels (N = 6, 30%) and erosions/ulcerations (N = 1, 5%).

Poikiloderma, which by definition encompasses telangiectasias, dyspigmentation and atrophy, was found in eleven patients (38%) and palmar papules in four patients (14%).

Dermoscopic data about Gottron papules, poikiloderma and palmar papules is presented in supplementary Table S1 and Figure 3.

Several unusual findings which deserve attention were also noticed. Four of the patients had auricular lesions (prominent telangiectasias, venous lake-like structures, erosions). One patient presented with significant perifollicular erythema on the body and extremities (supplementary Table S1 and Figure 3).

Conclusions
Periungual changes are a well-known marker for cutaneous affection in DM. As a standard practice, periungual lesions are examined via NFC. NFC pattern in DM is generally similar to this found in systemic sclerosis patients and therefore is referred to as a “scleroderma-like pattern”. NFC represents a valuable tool for the clinician as studies confirm that changes in nail-fold capillaries reflect disease activity in...
Figure 2. (A and B) enlarged tortuous capillaries. (C and D) Tufting (purple arrows), peripilar casts (blue arrows), perifollicular pigmentation (gray arrow). (E) Interfollicular scales. (F) Interfollicular pigmentation. (G) Vascular lake-like structure. (H) Bushy capillaries. (I) Perifollicular erythema. (J) Punctuate hemorrhages. (K) Broken hairs; (L) Pigtail hairs.

DM [8,9]. Data on periungual dermoscopy in DM patients is scarce and it is unclear whether dermoscopy might be used as a prognostic method for disease activity, in the same way as NFC, in those patients.

Our dermoscopic findings correspond roughly to those reported in the literature [10-12]. Most of the patients presented with scleroderma-like pattern suggestive for active disease. The most frequent nailfold dermoscopy features were respectively enlarged or giant capillaries and microhemorrhages. The enlarged/giant capillaries are regarded as an abnormal angiogenic response, secondary to peripheral ischemia. Hemorrhages most probably result from capillary injury caused by ischemia-reperfusion. Signs of early (disorganization of the normal capillary architecture) or late scleroderma-like pattern (large avascular areas/ loss of capillaries and ramified/bushy capillaries) were less frequent in our patient group.

Scalp involvement is a generally overlooked clinical characteristic of DM hence its actual frequency remains unrecognized. In the majority of manuals and review articles scalp DM is described as an erythematous, scaly and sometimes pruriginous condition of the scalp, resembling seborrheic dermatitis or psoriasis. Often nonscarring alopecia is also present [13-15]. We found only one study that examines scalp dermoscopy in DM patients [16]. In this study the authors performed trichoscopy on 31 patients with DM and concluded that in their patient group the most consistent finding was the presence of enlarged capillaries (71.4%), followed by peripilar casts (57.1 %) and tufting, and interfollicular scaling (50%). Our results demonstrated predominance of the same dermoscopic features - enlarged tortuous capillaries in fourteen patients (64%), peripilar casts and tufting in eight patients (36%), interfollicular scales in eleven patients (50%). In addition, we detected some hair shaft abnormalities (broken hairs, pigtail hairs) in the absence of other conditions that may present with such hair defects. We did not find any previous publications about hair shaft abnormalities in patients with DM.

Enlarged capillaries are a trichoscopic finding characteristic for connective tissue diseases. They can be easily differentiated from other vascular patterns, such as prominent arborizing vessels in seborrheic dermatitis or twisted capillary loops in psoriasis [17].

Hair tufting usually is regarded as a sign of scarring alopecia. The presence of more than six hairs suggests a
diagnosis of folliculitis decalvans. Hair tufts in lichen planopilaris contain fewer than six hairs (small tufts of four to five hairs)\textsuperscript{17}. For the purpose of this study, we consider tufting as more than 3 hair shafts emerging together from the same follicular opening, similarly to inflammatory scalp diseases.

Tufts tend to be surrounded by peripilar casts or tube-like layers of scales enclosing the hair shafts. The latter are also considered indicative of scarring alopecia [17].

Broken hairs are relatively non-specific and are seen in a variety of scalp diseases, such as alopecia areata, trichotillomania, tinea capitis, and trichorrhexis nodosa. In alopecia areata, broken hairs may develop by two mechanisms. One is inflammation-driven transverse fracture of terminal hair shafts and the other, rapid regrowth of incompletely destroyed hair shafts [14].

Pigtail or circular hairs appear as a result from fast hair regrowth before full recovery of the hair follicle. They are considered typical for alopecia areata although sometimes found in cicatricial alopecia [14].

In the expert consensus on dermoscopic parameters in general dermatology the topic about scalp dermoscopy is not addressed. Further prospective studies are needed to elaborate a guideline for evaluation of trichoscopic features in inflammatory diseases, especially considering rare diseases such as DM [1].

Dermoscopic picture of Gottron papules and Gottron sign is nonspecific. Irregular capillaries and scales on an erythematous background could be easily visualized. However, single peculiar cases are described. Hasegawa reported the presence of punctuate hemorrhages, detected by dermoscopy, on the elbow of a patient with Gottron sign [11]. The same patient was positive for anti-melanoma differentiation-associated protein 5 (MDA-5) autoantibody and later-on developed a rapidly progressive interstitial lung disease. Hasegawa suggested that punctuate hemorrhages might be related to vascular injury in the context of the aggressive interstitial pneumonia. The correlation between anti-MDA 5 antibody specificity in DM patients and the presence of skin ulcers is well known. Despite that, ulcerative Gottron papules/Gottron sign are a rather rare phenomenon [18]. In our patient group we had a case with anti-MDA 5 autoantibodies who exhibited ulcerated Gottron papules, noticeable

Figure 3. (A) Ulcerative Gottron papules. (B and C) Dermoscopy of Gottron papules. Note the circular appearance of the enlarged vessels in (C). (D) Clinical (D) and dermoscopic pictures of palmar papules (E-G). Note how palmar papules are located on the two opposite sides of the joint. (H) Poikiloderma on dermoscopy. (I) Perifollicular erythema on dermoscopy. (J) Auricular erosions. (K and L) Telangiectasias and vascular lake-like structures of the auricle on dermoscopy.
by naked eye, along with ulcerations all over the body and extremities (Figure 3).

Palmar papules or inverse Gottron papules are tender and often painful lesions on palmar surfaces with a predilection towards the metacarpal and interphalangeal joints. They are described also as a part of the MDA-5 antibody phenotype. Sometimes they are two separate papules on the two opposite sides of the joint [19]. Dermoscopy of palmar papules is virtually unexplored. In our patient group we had four patients with palmar papules examined by dermoscopy. We noticed the presence of dotted vessels on an erythematous base, sometimes with an orange hue. Scales were also observed (Figure 3). Palmar papules are considered a result of vasculopathy as histopathological data from previous studies demonstrates vasculopathy of small and medium-sized dermal vessels [19]. We did not perform skin biopsy of palmar papules. Interestingly, only one of our cases had MDA-5 autoantibodies in the serum. The other three were positive for transcriptional intermediary factor 1 gamma (TIF1-γ), small ubiquitin-like modifier activating enzyme (SAE1) and Mi-2 Beta autoantibodies, respectively.

Poikiloderma in DM is often a late finding. Typical distribution involves the sun-exposed skin of the neck and chest (V-sign) or the sun-protected skin of the upper back (shawl sign) and lateral thighs (holster sign). Seldom, it might have a more generalized character [20]. Dermoscopy enables better visualization of the three distinctive components, forming poikiloderma - cutaneous atrophy, telangiectasias, and macular pigmentary changes (Figure 3).

Anthelix/helix violaceous macules, erythematous auricular papules and even small ulcerations of the ears have been described previously in association with anti - MDA 5 antibody phenotype and have been proposed as a prognostic marker for fatal pulmonary disease [21-23]. The latter findings might be explained by an underlying vasculopathy. As tempting as it may seem to bind the auricular involvement with a particular autoantibody profile, we do not consider that ears, as a target organ in DM, are specifically affected only in patients with anti MDA-5 antibodies. In our opinion, auricular involvement is a known, although rarely noticed and little studied aspect of the clinical picture in DM [24]. In our study group, we have three patients with prominent auricular telangiectasias and one patient with both auricular vascular lake-like structures, and erosions (Figure 3). As the patient with auricular erosions is TIF1-γ positive, we suggest that in her case a different pathogenetic mechanism, other than vasculopathy, might be implicated in erosion formation. A possible interpretation might be a vacuolar degeneration of the basal layer of the epidermis.

Notable perifollicular erythema on the skin of the body and extremities was observed in one patient. The patient had a darker skin color (type IV according to Fitzpatrick classification (Figure 3).

The use of dermoscopy for clinical evaluation of skin lesions in DM enhances diagnostic accuracy and elucidates poorly known characteristics of the disease.

The present study had some obvious limitations due to its small sample size. Larger studies could help to distinguish clinical and dermatoscopic hallmarks in various subtypes of DM. The role of dermoscopy as a prognostic tool for disease activity and outcome in patients with DM remains to be investigated.

References


Cutaneous Manifestations and Their Corresponding Dermoscopic Features in Patients with Dermatomyositis

Joana Pozharashka, Ljubka Miteva, Lyubomir Dourmishev
### Table S1. Cutaneous manifestations and their corresponding dermoscopic features in 29 patients with dermatomyositis

<table>
<thead>
<tr>
<th>Periungual affection</th>
<th>Scalp dermatomyositis</th>
<th>Gottron papules</th>
<th>Palmar papules</th>
<th>Poikiloderma</th>
<th>Auricular skin changes</th>
<th>Perifollicular erythema the body</th>
<th>Dermoscopic features</th>
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<td>n=20 (69%)</td>
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* > 2 microhemorrhages per digit or confluent hemorrhagic zones; ** Tufting with > 3 hair shafts emerging together from the same follicular opening
Introduction:
It has been reported that the use of oral isotretinoin may have positive and negative effects on the course of COVID-19 and the risk of transmission.

Objectives:
The purpose of our study is to evaluate how our patients that took oral isotretinoin during the pandemic were affected by COVID-19.

Methods:
The clinical processes of moderate-to-severe acne vulgaris patients between March 2020 and February 2021 were evaluated.

Results:
Of 102 moderate-to-severe acne patients, 67 were using oral isotretinoin and 35 were using a topical treatment. Of 27 patients who tested positive for COVID-19, 16 (59.3%) were using oral isotretinoin and 11 (40.7%) were using topical treatment, there was no statistical difference in the rates of COVID-19 positivity between the two groups (P = 0.412). The rates of positive tests for COVID-19 were similar between contacted patients of two groups (P = 0.391). Loss of smell/taste was lower in patients using oral isotretinoin compared to patients receiving topical treatment (46.7% and 72.7%, respectively.). Headache symptoms were less common in patients using oral isotretinoin (P = 0.047).

Conclusions:
The use of oral isotretinoin did not cause an increase or decrease in the risk of COVID-19 transmission. The patients using oral isotretinoin had a lower incidence of taste/smell loss and headache.
Introduction
The coronavirus disease 19 (COVID-19) pandemic was declared by the World Health Organization in March 2020, and COVID-19 was the leading cause of death in many countries in 2020 [1]. No specific treatment has yet been found for COVID-19. In addition, as in other branches of medicine, the positive and/or negative effects of the drugs we frequently use in dermatology on the course of COVID-19 remain unclear.

Oral isotretinoin (13-cis-retinoic acid), a synthetic analog of vitamin A, is a first-generation retinoid used for the treatment of acne vulgaris [2]. Nasal mucosal dryness is observed in two-thirds of patients during oral isotretinoin treatment [3].

The COVID-19 agent SARS-CoV-2 enters the human body through Angiotensin-Converting Enzyme-2 (ACE2) receptors. ACE-2 receptor expression was found in the basal layer of nonkeratinized squamous epithelium in the nasal mucosa. Isotretinoin has the effect of revealing ACE-2 receptors by causing nasal mucosa dryness and down-regulating ACE-2 receptors at the same time [4-6]. Biological processes showing the pharmacological functions of vitamin A for the treatment of COVID-19 have been defined and its therapeutic mechanisms have been proven by signaling pathways and it is thought that it can be used in the treatment of COVID-19 [7]. However, some authors suggested that COVID-19 is a hypervitaminosis of vitamin A and that all drugs metabolized in the liver should be discontinued [8].

Objectives
According to these data in the literature, the effects of oral isotretinoin, a vitamin A derivative, on the transmission and course of COVID-19 are not clear. The aim of our study is to evaluate whether the use of oral isotretinoin affects the findings and symptoms of COVID-19 and the risk of transmission.

Methods
Our study was a retrospective, descriptive and cross-sectional study. The clinical processes of moderate-to-severe acne vulgaris patients aged 16 years and older who were followed up in our clinic between March 2020 and February 2021 and using oral isotretinoin at a dose of 0.5-1mg/kg or topical treatment (patients who do not accept systemic treatment), were evaluated.

The data form was filled via file scanning, during control examination, or by teleconference interview method. In the data, form followings were questioned: patients age, gender, body mass index, treatment received, disease severity, smoking, additional disease, additional treatments, pneumococcal and influenza vaccines, history of contact with someone with COVID-19, whether patients had COVID-19, if they had, symptoms, treatment of choice (without treatment, with medication at home, inpatient, in intensive care), whether there were any sequelae.

The obtained data were transferred to the computer. SPSS version 20.0 statistical package program was used in the analysis of the data. In the representation of the descriptive statistics of the study, mean ± standard deviation (SD), minimum-maximum values for continuous numerical variables, number (N), and percentage (%) were used for categorical variables. Pearson chi-square and Fisher tests were used to compare categorical variables. According to the normality evaluation made by Kolmogorov-Smirnov and Shapiro-Wilk tests; Parametric tests (paired sample t-test and t-test in independent groups) were used where continuous variables fit the normal distribution, and nonparametric tests (Mann-Whitney U test, Kruskal Wallis test) were used where they did not fit the normal distribution. Statistical significance level was accepted as P < 0.05.

Results
The study included 102 moderate-to-severe acne patients aged 16 years and older who were followed up and treated in our clinic, using oral isotretinoin at a dose of 0.5-1mg/kg or topical treatment (topical retinoid or topical benzoylperoxide plus clindamycin) for at least two months. The clinical processes between March 2020 and February 2021 were evaluated.

Of the 67 patients who took oral isotretinoin during the pandemic, 52 (77.6%) were female and 15 (61%) were male, mean age was 22.64 ± 6.62. Of 35 patients who used topical treatment, 19 (54.3%) were female and 16 (61%) were male, the mean age was 25.74 ± 8.16.

Twenty (74.1%) of the women and 7 (25.9%) of the men had a history of 27 COVID-19 positivity confirmed by polymerase chain reaction (PCR) in the nasal swab sample. The mean age of those who were positive for COVID-19 was 24.88 ± 8.65, and there was no statistical difference in age and gender between those who were positive for COVID-19 and those who were negative for COVID-19 (P = 0.773 and P = 0.556, respectively). There was no statistical difference between COVID-19 positive and COVID-19 negatives in terms of body mass index (BMI) average, smoking, additional disease status, acne severity, pneumococcal and influenza vaccination status (Table 1).

Of the 27 patients who were positive for COVID-19, 16 (59.3) were using oral isotretinoin and 11 (40.7%) were using a topical treatment. There was no statistical difference in COVID-19 positivity rates between patients using oral isotretinoin and patients using topical treatment (P = 0.412).
Considering the rates of COVID-19 transmission after contact with a COVID-19 positive person, COVID-19 positivity in 14 of 29 patients, who were using oral isotretinoin and came into contact with someone that tested positive for COVID-19 was confirmed by PCR test; COVID-19 positivity in 11 of 18 patients who were using the topical treatment and came into contact with someone that tested positive for COVID-19 was confirmed by PCR test. There was no statistical difference in the rates of being positive for COVID-19 between contacted patients using oral isotretinoin and contacted patients using topical treatment ($P = 0.391$).

Of the 27 patients who were positive for COVID-19, 26 had symptoms, only one patient using oral isotretinoin was asymptomatic, and there was no statistical difference in the rates of asymptomatic COVID-19 positivity between patients using oral isotretinoin and patients using topical treatment ($P = 0.593$).

In order of frequency, the symptoms associated with COVID-19 were: taste\smell loss (15), headache (13), fever (12), malaise (12), arthralgia/myalgia (11), cough (8), sore throat (6), shortness of breath (4). There was no statistical difference between patients using oral isotretinoin and patients using topical treatment in terms of the incidence of symptoms other than headache. Headache was seen at a lower rate in patients using oral isotretinoin compared to those using topical treatment (33.3%, 72.7%, respectively), and there was a statistically significant difference ($P = 0.047$). Taste\smell loss developed in 7 (46.7%) of 16 COVID-19-positive patients using oral isotretinoin and 8 (72.7%) of 11 COVID-19-positive patients using topical treatment, but there was no statistical difference ($P = 0.246$) (Table 2).

Among the gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (dyspnea, chest pain) associated with severe COVID-19, only shortness of breath was seen in 4 of our patients, other severe symptoms were not encountered. Dyspnea was observed in one patient (6.7%) using oral isotretinoin and 3 (27.3%) patients receiving topical treatment. There was no statistically significant difference between the two groups ($P = 0.279$).

No patient with COVID-19 needed hospitalization or intensive care. Of the 16 COVID-19-positive patients who took oral isotretinoin, 10 recovered with medical treatment at home and 6 without treatment. All 11 COVID-19-positive patients who received topical treatment recovered with medical treatment at home. There was no statistical difference between the two groups in terms of the need for medical treatment ($P = 0.054$).

Six of the patients with COVID-19 had partial taste\smell loss that continued 1 month after they had the disease.

| Table 1. Sociodemographic and clinical characteristics of the acne vulgaris patients (comparison between COVID-19-positive and negative patients) |
|---------------------------------|---------------------------------|------------------|
|                                | COVID (+) mean ± SD / N (%)     | COVID (-) mean ± SD / N (%) | P      |
| Age                            | 24.88 ± 8.65                   | 23.28 ± 6.76      | 0.773a |
| BMI                            | 23.25 ± 2.88                   | 22.64 ± 3.01      | 0.201a |
| Gender                         |                                 |                  |       |
| Male                           | 7 (25.9)                       | 24 (32.0)         | 0.556b |
| Female                         | 20 (74.1)                      | 51 (68.0)         |        |
| Smoking                        |                                 |                  |       |
| Yes                            | 4 (14.8)                       | 15 (20.0)         | 0.553b |
| No                             | 23 (85.2)                      | 60 (80.0)         |        |
| Additional disease             |                                 |                  |       |
| Yes                            | 1 (3.7)                        | 7 (9.3)           | 0.678b |
| No                             | 26 (96.3)                      | 68 (90.7)         |        |
| Pneumococcal vaccine           |                                 |                  |       |
| Yes                            | 0 (0.0)                        | 4 (5.3)           | 0.571b |
| No                             | 27 (100)                       | 71 (94.7)         |        |
| Influenza Vaccine              |                                 |                  |       |
| Yes                            | 1 (3.7)                        | 2 (2.7)           | 0.607b |
| No                             | 26 (96.3)                      | 73 (97.3)         |        |

BMI = body mass index; SD = standard deviation.

aMann-Whitney u test; bChi-squared or Fisher test for the comparison between the groups.
thanks to their antioxidant and surfactant-mediated properties [9]. We did not see ARDS symptoms in any of our patients. We could not associate this with the protective use of oral isotretinoin, because our patients had a low mean age and a very low rate of possible risk factors for ARDS.

Gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (shortness of breath, chest pain) have been associated with severe COVID-19 [10]. Severe COVID-19-associated dyspnea was seen at a lower rate in patients using oral isotretinoin compared to patients receiving topical treatment (6.7% vs 27.3%, respectively), we thought that this might be related to the protection of oral isotretinoin against severe COVID-19, but we did not detect a statistically significant difference (P = 0.279).

ACE2 has been shown to be a functional receptor for SARS-CoV to enter host target cells [11]. ACE2 receptor expression has been found in the basal layer of the squamous epithelium in the nasal mucosa. The use of oral isotretinoin, which causes dryness in the nasal mucosa, causes mucosal fragmentation, and may facilitate the adhesion of the coronavirus to the nasal mucosa by exposing the basal layer [4,5]. On the other hand, since isotretinoin is one of the strongest down-regulators of ACE-2 receptors, it was thought that the use of isotretinoin may be protective against the transmission of COVID-19 in that it reduces the possibility of cellular entry of the virus [6]. To evaluate these hypotheses, we looked at the rates of being positive for COVID-19 after contact with a COVID-19 (+) person, and we did not find any difference in the rates of being COVID-19-positive between contact patients using oral isotretinoin and contact patients using topical treatment (P = 0.391). Öğüt et al also found that oral isotretinoin treatment was not associated with an increased risk of contracting COVID-19 [12]. These results suggest that oral isotretinoin use increases the risk of transmission by exposing ACE2 receptors, while reducing the risk of transmission by down-regulating ACE2 receptors, leading to a similar risk of transmission with people who do not use isotretinoin.

2 (12.5%) were receiving oral isotretinoin and 4 (36%) were receiving topical treatment. There was no statistical difference between the patients using oral isotretinoin and the patients using topical treatment in terms of taste/smell loss sequela (P = 0.350).

Discussion

It has been reported that the use of oral isotretinoin may have positive and negative effects on the course of COVID-19 and the risk of transmission (Table 3).

Mawson et al. found that COVID-19 disease is very similar to an endogenous form of a hypervitaminosis of vitamin A, that liver damage caused by the SARS-CoV-2 virus causes toxic concentrations of retinoic acid and stored retinyl esters to be released into the circulation, including the lungs, heart, blood vessels, and skin, without binding to protein. They claimed it caused damage to organs. They recommended that treatment strategies focus on reducing circulating retinoid concentrations. They argued that all nonessential drugs that are metabolized in the liver should be discontinued, and also that all drugs that damage the liver should be avoided during the acute phase of treatment [8]. However, the patients using oral isotretinoin included in our study did not need hospitalization or intensive care even though they continued their medication when they became COVID-19-positive.

Retinoic acid and carotenoids exert many physiological effects, along with the enhancement of T-cell function, which develops an inducible immune response against pathogens such as viruses [9]. Bioinformatics computational findings showed that vitamin A has anti-viral, anti-inflammatory, and immunomodulatory effects through different biological processes and cell signaling pathways. As a result of these findings, the therapeutic mechanisms of vitamin A for the clinical treatment of COVID-19 have been defined [7]. Therefore, contrary to Mawson et al, it is thought that vitamin A derivatives may have a protective role in the pathogenesis of ARDS, which is a complication of severe COVID-19 cases, thanks to their antioxidant and surfactant-mediated properties [9]. We did not see ARDS symptoms in any of our patients. We could not associate this with the protective use of oral isotretinoin, because our patients had a low mean age and a very low rate of possible risk factors for ARDS.

Gastrointestinal (nausea, vomiting, abdominal pain) and respiratory symptoms (shortness of breath, chest pain) have been associated with severe COVID-19 [10]. Severe COVID-19-associated dyspnea was seen at a lower rate in patients using oral isotretinoin compared to patients receiving topical treatment (6.7% vs 27.3%, respectively), we thought that this might be related to the protection of oral isotretinoin against severe COVID-19, but we did not detect a statistically significant difference (P = 0.279).

ACE2 has been shown to be a functional receptor for SARS-CoV to enter host target cells [11]. ACE2 receptor expression has been found in the basal layer of the squamous epithelium in the nasal mucosa. The use of oral isotretinoin, which causes dryness in the nasal mucosa, causes mucosal fragmentation, and may facilitate the adhesion of the coronavirus to the nasal mucosa by exposing the basal layer [4,5]. On the other hand, since isotretinoin is one of the strongest down-regulators of ACE-2 receptors, it was thought that the use of isotretinoin may be protective against the transmission of COVID-19 in that it reduces the possibility of cellular entry of the virus [6]. To evaluate these hypotheses, we looked at the rates of being positive for COVID-19 after contact with a COVID-19 (+) person, and we did not find any difference in the rates of being COVID-19-positive between contact patients using oral isotretinoin and contact patients using topical treatment (P = 0.391). Öğüt et al also found that oral isotretinoin treatment was not associated with an increased risk of contracting COVID-19 [12]. These results suggest that oral isotretinoin use increases the risk of transmission by exposing ACE2 receptors, while reducing the risk of transmission by down-regulating ACE2 receptors, leading to a similar risk of transmission with people who do not use isotretinoin.
During the course of COVID-19, the most common clinical symptoms were reported as fever, cough, headache, and sore throat, in decreasing order of frequency [13]. In our patients, this order was taste/smell loss, headache, fever, malaise, arthralgia/myalgia, cough, sore throat, and shortness of breath. We found that the headache symptom decreased with the use of oral isotretinoin (P = 0.047). Various mechanisms have been described for headaches due to COVID-19. The first of these mechanisms has been reported to be the invasion of the trigeminal nerve endings of the virus that is bound to ACE2 receptors in the nasal cavity. We thought that the use of oral isotretinoin may cause a less frequent occurrence of headache due to COVID-19, with the down-regulating effect of isotretinoin on ACE2 receptors [6,11,14].

Although taste/smell loss is one of the most commonly known symptoms of COVID-19 in the non-medical community, its incidence varies between 0% and 98% [15]. We found the rate of taste/smell loss to be 55%, this rate was higher in patients using a topical treatment (72.7%).

It has been reported that the loss of taste/smell is resolved in most cases within an average of 14 days from the full recovery of COVID-19. However, in some of the patients, it was observed that the loss of taste/smell partially improved after months or did not improve at all [15].

It was found that retinoic acid treatment in mice increased the number of macrophages expressing retinoic acid receptors, and this increase was associated with a faster recovery of olfactory function [16,17]. Oral isotretinoin has been shown to improve the sense of smell in humans according to the olfactory function test evaluated before starting oral isotretinoin treatment and at the third month of treatment [18]. According to the data of our study, loss of smell/taste was lower in patients using oral isotretinoin compared to patients receiving topical treatment (46.7% and 72.7%, respectively), this may be related to the improvement of the sense of smell by oral isotretinoin use, but we found no statistically significant difference (P = 0.246). Partial loss of taste/smell, which persisted 1 month after recovery, was lower in patients using oral isotretinoin compared to patients receiving topical treatment (12.5% and 36%, respectively), which may be related to the faster recovery of olfactory function by isotretinoin, but again, no statistical difference was observed (P = 0.350). The main weakness of this study is that the small number of patients. Smell/taste loss levels could not be evaluated objectively because it is a retrospective study.

In conclusion, the use of oral isotretinoin did not cause an increase or decrease in the risk of COVID-19 transmission. Headache symptom was seen less frequently in oral isotretinoin users. In patients using oral isotretinoin, the rates of taste/smell loss were lower, although not statistically significant. The rates of complete recovery of taste/smell loss were higher in oral isotretinoin users, although it was not statistically significant.

### Table 3. Possible associations between oral isotretinoin and COVID-19

<table>
<thead>
<tr>
<th>COVID-19 transmission risk and oral isotretinoin use</th>
<th>Oral isotretinoin may increase the risk of transmission by exposing ACE-2 receptors in the nasal mucosa.</th>
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<tbody>
<tr>
<td>Severe COVID-19 and use of oral isotretinoin</td>
<td>Because COVID-19 disease resembles an endogenous form of hypervitaminosis of vitamin A, the use of oral isotretinoin may worsen the disease severity.</td>
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<tr>
<td>COVID-19 treatment and oral isotretinoin use</td>
<td>Oral isotretinoin can be used in the treatment of COVID-19 as it has anti-viral, anti-inflammatory, and immunomodulatory effects.</td>
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<td>Symptoms due to COVID-19 and use of oral isotretinoin</td>
<td>Oral isotretinoin can alleviate COVID-19-related headache with its down-regulating effect on ACE-2 receptors and anti-inflammatory-immunomodulatory effects.</td>
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Since oral isotretinoin increases the sense of smell and improves the lost sense of smell, it can reduce the level of taste-smell loss due to COVID-19 and accelerate its recovery.

### References


Objectives: to evaluate clinical chart of patients with IH who had cardiologic evaluation before propranolol therapy and to compare our findings with literature data.

Introduction: Some studies have assessed the incidence of heart defects in children suffering from infantile hemangioma (IH) treated with propranolol, showing a possible higher prevalence of cardiac abnormalities in this group of patients.

Methods: We retrospectively reviewed clinical charts of children with infantile hemangiomas referred to our dermatologic division from 2016 to 2021, who underwent our pediatric cardiology protocol screening before starting propranolol therapy.

Results: A total of 60 infants were enrolled. Electrocardiograms were available for all the patients and echocardiography for 50/60 (83.3%) children. Electrocardiogram didn’t reveal any alterations in most cases (pathologic in 2/60 ones, 3.3%) while echocardiograms revealed findings in 31/50 (61.7%) patients. Of these, persistent foramen ovale, which was found in 14/50 patients (28%), was considered as non-pathologic. Interatrial septal defects were the main pathological finding in 15/50 patients (30%), as single defect or in association with other abnormalities.

Conclusions: Our study confirms the presence of a higher rate of cardiologic findings in patients with infantile hemangioma evaluated before starting oral propranolol, compared to the known rate of those defects in healthy newborns. We also confirm that interatrial septal defects are the most frequent pathologic finding with a higher prevalence compared to published studies. Large prospective studies are needed to clarify a possible association of pathological cardiac findings in all patients with infantile hemangiomas and thereafter to evaluate the possible effect of propranolol therapy on these defects during time.
Introduction

Infantile hemangiomas (IH) are the most common benign tumor in infancy with an incidence between 5% and 10% in different population [1]. Usually, they undergo a natural regression and do not require any treatment, therefore a “wait and see” approach is considered the best option for most affected newborns. However, in a subset of patients, IH can be worrisome for the risk of functional or aesthetic consequences. In 2008, following a serendipitous clinical observation, oral propranolol has been shown to be highly effective in the treatment of IH since then this drug has been widely used as galenic formulation. In 2014 an oral formulation has been licensed in Europe and oral propranolol is now considered the gold standard for the therapy of complicated hemangioma. In our hospital patients starts treatment with oral propranolol at 1 mg/kg in 2 divided doses under pediatric observation for 2 hours. The dose is then gradually increased over the subsequent weeks following the standard protocol of stepping the dose up to 2 mg/kg daily the second week of treatment and up to 3 mg/kg daily the third week. Another possibility is to follow an “at home” dose escalation strategy with telemedicine follow-up [2]. We developed and applied this protocol during the lock-down phase related to the SARS-CoV-2 pandemic, but we now offer this possibility to all families aiming to reduce the number of hospital visits. The therapy is usually continued until the 12th month of life with rare exceptions, such as rapid improvement of the lesion or extensive/recurrent IH in which therapy length could be respectively reduced or prolonged.

Potential side effects of propranolol include bradycardia, hypotension, hypoglycemia, bronchospasm and sleep disturbances. All these are rare and usually not lead to discontinue the treatment [3]. Nevertheless in order to exclude congenital hidden heart disease which would contraindicate propranolol administration and to identify children in whom the drug may potentially induce side effects before starting therapy a general evaluation it is usually performed by a pediatrician. However, in our hospital, while not specifically requested in routine practice patients with IH who need propranolol therapy are also evaluated by a pediatric cardiologist [4]. Our cardiology unit offers a care package in which next to cardiologic examination also an electrocardiogram (ECG) and echocardiography (ECHO) are performed in all children.

Objectives

Few published studies have shown a raised incidence of cardiac defects in patients with IH [5,6]. We then decided to retrospectively evaluate clinical chart of patients with IH who had cardiologic evaluation before propranolol therapy and to compare our findings with literature data.

Methods

Study Population

We retrospectively evaluated clinical charts of all children with IH requiring propranolol therapy at our countryside hospital between January 2016 and January 2021. According to our protocol patients referred to our outpatient service for IH undergo a complete pediatric and cardiology evaluation including ECG and ECHOcardiogram before starting therapy. Children with segmental IH are also investigated with magnetic resonance imaging (MRI) to exclude the association with other congenital vascular malformations. Two-dimensional, M-mode, continuous Doppler and color Doppler echocardiography is performed using iE33 Philips Medical Ultrasound System equipped with a high-frequency phased-array sector scan probe (S8) and second-harmonic technology. All the evaluations are performed by the same senior cardiologist (AA) and comprise a complete sequential segmental analysis for each child. Atrial septal defect is diagnosed when a shunt through the interatrial septum can be documented by color flow mapping in subcostal four-chambers and sagittals views. We do not record as atrial septal defect (ASD) the interatrial communications less than 4 mm in length detected in infants less than 3 months of age. According to the local ethical board, informed consent was not required, since it was retrospective study with anonymous data.

Statistical Analysis

Data were analyzed by SPSS Statistics, 24.0 statistics software. Categorical variables and frequencies were compared by means of the χ² test or Fisher test, as appropriate. Quantitative variables were reported as median and interquartile range (IQR) and compared by means of nonparametric tests (Mann–Whitney U). A P value of 0.05 was considered to indicate statistical significance.

Results

During this study period 950 children with IH presented in our clinic. Of these, 60 (6.3%) patients with IH were treated with oral propranolol in the study frame time and all clinical charts were reviewed to retrieve relevant data. The median corrected age at first evaluation was 3 months (IQR: 2-5). Seventy percent of cases were female (42/60), and the median gestational age at delivery was of 40 weeks (IQR: 36-40). In our population, 18/60 (30%) infants were born preterm. Regarding the localization of IH, in 40/60 (66.7%) children was on the head and among these in 7/40 (17.5%) were “Cyrano” IH. 12/40 (30%) were on the scalp, 5/40 (12.5%) on the cheek (2 of these were diagnosed as
PHACE syndrome after MRI imaging), 4/40 (10%) on the ears and 12/40 (30%) on the forehead. In 9/60 (15%) IH were localized on the lower and upper arms including shoulder, 7/60 (11.7%) on the trunk, 1/60 (1.7%) on the diaper area and 3/60 (5%) presented with multiple IH. All data are summarized in Table 1.

Data about cardiologic screening in particular for ECG examination were available for all the patients and almost all (58/60, 96.7%) presented a regular ECG for age. Only 2 patients presented a right ventricular overload.

Ultrasound examination was available for 83.3% (50/60) of the patients. Among these, 19/50 (38%) didn’t reveal any alterations and 14/50 (28%) had a persistent foramen ovale, a common finding considered to be non-pathological. Pooling together these two groups 33/50 patients (66%) had a normal ultrasound, while the remaining 17/50 (34%) showed significant cardiac alterations. The most frequent cardiac defect was an isolated interatrial septal defect observed in 13/17 (26% of all patients). Moreover, one patient had an interatrial septal defect associated with persistent left superior vena cava and another one associated with pulmonary stenosis. Finally, one patient had a patent ductus arteriosus and in another one a flow acceleration in the aortic arch was seen. The median age (corrected for gestational age) at which the interatrial septal defect was observed was 3 months (IQR: 2-4); 9 out of these were observed at ≥ 3 months of age (18% of all patients) and 6 at < 3 month (12% of all patients). Of the 9 patients observed at ≥ 3 months, 8 presented an interatrial defect > 3 mm.

The median defects diameter was 4 mm (IQR: 3-6) with an ostium secundum type and left to right shunt in all patients. The 2 patients with abnormal ECG didn’t present any ultrasound alterations.

A possible association of abnormal cardiac findings with demographic or clinical variables was evaluated. However, no statistically significant association was found with age (p = 0.354), sex (P = 0.757), gestational age (P = 0.480), prematurity (p = 0.329) or hemangioma localization (P = 0.494).

None of the ECG and ECHO findings were considered contraindications for systemic propranolol treatment.

### Conclusions

Since systemic propranolol therapy was introduced for the treatment of IH several protocols of administration and monitoring have been proposed in order to reduce the potential risks related to the therapy [1,6]. Pretreatment evaluation is warranted both to exclude congenital hidden heart disease which would contraindicate propranolol administration and

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N = 60)</th>
</tr>
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<tbody>
<tr>
<td>Age starting propranolol and cardiac screening</td>
<td>3 months (IQR: 2-5)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>42</td>
</tr>
<tr>
<td>Preterm</td>
<td>18</td>
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<tr>
<td>Gestational age</td>
<td>40 weeks (IQR: 36-40)</td>
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<tr>
<td>IH localization</td>
<td></td>
</tr>
<tr>
<td>• face</td>
<td>40</td>
</tr>
<tr>
<td>• trunk</td>
<td>7</td>
</tr>
<tr>
<td>• arms</td>
<td>9</td>
</tr>
<tr>
<td>• diaper</td>
<td>1</td>
</tr>
<tr>
<td>• multiple IH</td>
<td>3</td>
</tr>
<tr>
<td>Cardiological findings</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram (60/60 available)</td>
<td>58/60 no pathologic findings</td>
</tr>
<tr>
<td>Echocardiogram (50/60 available)</td>
<td></td>
</tr>
<tr>
<td>• no findings</td>
<td>19/50</td>
</tr>
<tr>
<td>• persistent foramen ovale</td>
<td>14/50</td>
</tr>
<tr>
<td>• interatrial septal defect</td>
<td>13/50</td>
</tr>
<tr>
<td>• interatrial septal defect + patent ductus arteriosus</td>
<td>1/50</td>
</tr>
<tr>
<td>• interatrial septal defect + pulmonary stenosis</td>
<td>1/50</td>
</tr>
<tr>
<td>• flow acceleration in aortic arch</td>
<td>1/50</td>
</tr>
<tr>
<td>• persistent left superior vena cava</td>
<td>1/50</td>
</tr>
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</table>

IH = infantile hemangiomas; IQR = interquartile range.
to identify children in whom the drug may potentially induce side effects including bradycardia, hypotension, bronchospasm or hypoglycemia. Whether to perform ultrasound, ECG or simply a clinical examination is however controversial. The most recent literature underlines the lack of additional value of performing instrumental evaluations such as ECG as a pretreatment screening tool [7-11]. In our hospital a clinical protocol in which a complete pediatric and cardiological screening, including ECG and ultrasound, is usually performed in all patients as part of a specific care package. In line with previous studies, in our population we didn’t find any cardiac contraindications to start propranolol treatment. In particular ECG was performed in all the patients, but no significant findings were found thus confirming the low informative value of this exam. On the contrary some interesting data were derived from ultrasound heart examination. ECHO was available for 83.3% patients and in 38% of patients was normal. A persistent foramen ovale was found in 28% of patients and considered as a normal variant. The most frequent pathological abnormality was an interatrial septal defect that was present in 15/50 of patients (30%) either as an isolated finding (13/50 - 26%) with a presentation as ostium secundum type with left to right shunt or associated with a persistent left superior vena cava or pulmonary stenosis.

Few other studies have addressed this topic. In particular, Blei et al analyzed 239 patients and found 16% of interatrial septal defects, while Frongia et al analyzed 234 patients with only 8.1% of prevalence of this defect [5,6]. In any case, these studies clearly showed that in patients with IH there is a higher frequency of cardiac abnormalities compared with the reported incidence of congenital heart disease in the general population, which has been shown to range from 0.8% to 1.0% and going up to 7.5% only with the inclusion of other alteration such as patent foramen ovale [12-16]. Our study confirms the higher prevalence of cardiac abnormalities among patients with IH in particular of interatrial septal defect. The clinical significance of our findings is supported by the median age at observation and the median diameter of the defect which are in line with the criteria of inclusion by the median age at observation and the median diameter of the defect which are in line with the criteria of inclusion by the median age at observation and the median diameter of the defect [17]. The 3 months age as a cut-off to consider an ultrasound finding to be relevant is consistent with the median age at observation and the median diameter of the defect which are in line with the criteria of inclusion by the median age at observation and the median diameter of the defect (our median diameter was 4 mm) [17]. The 3 months age as a cut-off to consider an ultrasound finding to be relevant is because before this age the interatrial communications are common and account for 78% of the heart disease compared to 25% in older infants and children [18]. At the same time, it has been demonstrated that the incidence of spontaneous closure of interatrial communications before 3 months of age is about 60% and, in addition, interatrial defects of less than 3 mm undergo spontaneous closure in almost 100% of cases [17,18]. Our data shows that even considering only children older than 3 months (thus excluding children less than 3 months), the prevalence of ASD is anyway clearly greater than data reported in literature for general population (18% versus 0.8%-1%) [12-13].

The limited number of patients and the intrinsic limitations of retrospective studies does not allow us to draw a definitive conclusion however our study along with literature data seems to confirm that patients with IH have a substantially higher prevalence of congenital heart disease in respect to general population. Indeed, these data needs confirmation in larger prospective, multicenter, studies which should include all patients with IH to be evaluated at specific time points irrespectively of therapy with propranolol. Such a study will also be of interest to reveal a possible effect of propranolol therapy on the closure of ASD and also the significance and the possible value of IH as a clue to suspect the presence of a cardiac defect. In particular it would be of great importance to understand whether along with well-known syndromes such as PHACE a particular combination of characteristics such as dimension, number and/or localization could indicate a raised risk of cardiac disease [19].

References


Dermoscopy for Cutaneous Melanoma: Under the Eye of Both the Dermatologist and the Legal Doctor

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Worldwide, melanoma is the 20th most common cancer, with 287,723 estimated new cases (1.6% of all cancers) and 60,712 related deaths (0.6% of all cancer deaths) in 2018, and a five-year prevalence of 965,623 cases [1]. Cutaneous melanoma (CM) is by far the most common melanoma subtype and a potentially fatal disease. Early recognition is of utmost importance to improve the prognosis, since if melanoma is diagnosed at noninvasive stage, the patient will be treated by excision of the primary tumor, but if melanoma becomes invasive, the chance of recovery decreases as invasion thickness increases [2]. Given its dramatic rise in incidence, its predilection for middle-aged patients, and its ability to masquerade as a benign lesion, melanoma is easily misdiagnosed, providing a basis for malpractice claims [3,4].

Dermatoscopy, commonly referred as dermoscopy, is a noninvasive technique allowing microscopic visualization of subsurface skin structure not visible to the naked eye [5]. A trained user, through a hand-held microscope, equipped with a magnification lens and a light source (the dermatoscope), can appreciate the deeper primary morphology of cutaneous lesions beyond the gross morphologic features, such as size, shape, colors, contours, and topography. This approach improves the diagnostic accuracy for melanoma [6] and the observers confidence in their clinical diagnosis [7].

Unfortunately, even with dermoscopy, some melanomas remain clinically and dermoscopically indistinguishable from other lesions, such as seborrheic keratoses, whose suggestive features might be displayed in up to 18% of melanomas, vascular lesions and pyogenic granulomas, lichen planus-like keratoses, warts, dermatofibromas, ulcers and, finally, from melanocytic nevi, hence difficult to diagnose [8-16]. This is particularly true in patients with atypical mole syndrome, whose nevi share clinically some, or all, the features of CM (the ABCDs: asymmetry, border, irregularity, color variability, and diameter > 6 mm).

A strategy involves the dermoscopic follow-up of atypical lesions, through sequential digital dermatoscopy imaging, and excision only of those lesions that change over time [17].
The introduction of digital dermatoscopes or so-called video-dermatoscopes (VDS), the sequential digital dermatoscopy imaging (SSDI) and total body photography (TBP) are further options in the general digital progress within medicine and dermatology. These systems are equipped with high-resolution color video cameras that reveal monitor images obtained using non-polarized or polarized light. They achieve higher magnifications than most common hand-held dermatoscopes and simplify image acquisition, storage, organization, analysis, and retrieval. These techniques are appreciated and requested by the patients who, however, might do not fully understand the rational of the methods, often believing their nevi are being monitored because at risk of malignant evolution, especially the atypical ones [18]. Indeed, the actual risk of any given nevus of transforming into a melanoma has been estimated to be low, whereas the majority of melanomas appear to arise de novo [19], and “atypical” nevi are at no higher risk of developing into a melanoma; rather, the “atypical” nevus is more likely to actually be a melanoma whose dermoscopic features may not differ significantly at baseline from nevi [15].

A discrepancy between patients and physician’s expectations towards VDS and TBP might be even at the base of the doctor-patient relationship, and this is not without danger. The availability of monitoring during follow-up changes the clinician threshold for biopsy suspicious pigmented lesions, resulting in a fall in the sensitivity for melanoma at the first examination, to increase the specificity and the accuracy for melanoma detection at the next evaluation. There are 2 main approaches: short-term follow-up (3 months) is used to make a clinical decision about single, flat or slightly raised suspicious melanocytic lesion, lacking dermoscopic features of melanoma; while medium or long-term monitoring, generally restricted to patients with multiple nevi, mainly aims at comparison of multiple inconspicuous lesions over standard surveillance periods (usually 6 or 12 months) [20].

To work properly, this method of follow-up needs patients’ compliance with follow-up timing. Unfortunately, it has been proven that patients compliance strongly decreases with long-term control visits, with the risk of melanoma un-treatment [21–23], and we cannot exclude this is due to a misunderstanding and misconmunication between patient and physician about how the method works.

Moreover, the depth of invasion is the most critical prognostic factor of malignant melanoma, but dermoscopic findings do not allow a reliable evaluation of the tumor thickness, nor a sure distinction between an in situ and an early invasive phase [24–26] and, consequently, diagnosis remains only histopathological. The question is of more than academic interest because melanoma is a completely curable disease if diagnosed early, while still in situ. Once it becomes invasive, the diagnosis becomes easier but the best chance for recovery has been lost. It has been widely proven that sequential dermoscopy imaging detects mostly thin incipient melanomas [15,27,28] and patients with these lesions are generally considered to be at low risk for metastasis and melanoma-related death, but it is well known that a portion of this group will eventually experience disease recurrence and risk death from melanoma [29–32]. One can wonder if, comprehensively informed, a patient would rather opt for immediate surgical removal, sacrificing specificity over sensitivity. On the other hand, removal of all unusual-appearing nevi, especially in patients with multiple atypical nevi, is usually impractical.

The use of TBP might further facilitate the detection of new lesions, as well as visual changes in pre-existing lesions, by providing a comparative reference point of areas of skin for subsequent examinations [33].

During a dermoscopic and clinical visit, we might be tempted to feel that our conversation with a patient sufficiently ensures that the patient has freely and knowingly accepted the procedure. However, while dialogue is necessary, it is not sufficient for legally documenting informed consent, given that in some countries, Italy and Spain for example, the law stipulates that consent must be given by traceable means, such as in writing [34,35]. The informed consent doctrine has, in fact, three goals: (1) to include patients in the decision-making process; (2) to involve the patient in the choices that affect the psycho-physical aspect; and (3) to ensure the patient is aware of the potential benefits and hazards of the treatment [36].

In dermoscopy context, compared with the issue of patient’s follow-up in medicine as a whole, for the several aforementioned issues and regarding especially the third point, proper documentation of the care planning, with information about prognosis, follow-up, and therapeutic approaches, to which the patient consents, is fundamental in the reduction of litigation related to melanoma misdiagnosis, usually seen as diagnostic delay and illicit reduction of survival and/or quality of life. In medicolegal cases, a physician note may provide additional evidence that the physician met the applicable standard of care, while inadequate documentation may reduce the likelihood of a successful defense [3].

Of great interest, a recent pronunciation of the II Civil Section of the Genua Tribunal (n. 939/2017) discusses two of the main issue on diagnostic delay for melanoma: at first, the importance of written health records, to identify the followed diagnostic procedure and the proper information; secondly, the need of standard formation of dermatologist about dermoscopy, to avoid, in cases of doubtful lesions, “that there was not even observation with a dermatoscope” [37]. In addition to documentation, photography becomes more widespread in both general dermatological setting, and in dermoscopy, because specific part of the method;
photography, in fact, may directly impact patient care by allowing the clinician to detect changes in pigmented lesions. A proper patient’s disclosure over picture management must also be added in the medical records [38,39].

Hence, video-dermoscopy and sequential dermoscopy imaging, with their particular characteristics, might need a deep information and appropriate signed written consent [36].

At least in Italy, in litigations and trials regarding diagnostic delays of melanomas, the study of Lin et al is used to estimate the impact on the prognosis: in our opinion the article has to be considered with extreme caution, because only the rate of growth of the lesion, from a histopathological point of view, is investigated, so it is improper to directly convert this data into patients’ prognosis [40]. Consequently, dermatologists and hospitals might face medicolegal concerns for some months delay, even in case of small and likely in situ melanomas, if not properly diagnosed and followed [41]. Thus, implementing enough instruments and specialists is mandatory to guarantee optimal follow-up and to meet the patients’ needs and expectations. It is important to remember that the specificity for melanoma diagnosis at the second visit, however, increases only for those with experience with the method, hence the need for trained specialists [17,42]. Nowadays, TBP with standard VS is the best standard of care: to identify the best diagnostic tool for CM diagnosis means to define the parameter of the dermatologist diligence, namely, to exclude professional liability.

Beyond this information, it is critical to understand several key elements, clinical and medicolegal. Melanoma diagnosis remains difficult, with frequent misdiagnosis, so the definition of the dermoscopy “standard of care” and the identification of shared diagnostic guidelines is fundamental. To grant this “standard of care”, it is important to be wary of quick and “magical” solutions, in the era of online diagnoses, and to refer to renowned centers and specialists on melanoma, enhancing clinician professionalism. To avoid clinical and judicial delays, patients need to be informed about the aim of dermoscopy for CM diagnosis, and about the relevance of follow-up compliance. Moreover, lesion pictures and their storage are part of the diagnostic procedure: the patient must be properly informed, and he/she must properly disclose it.

In conclusion, the medicolegal gaze could be useful to the dermatoscopist, providing him with a different and better confidence in the method, assuring a greater patient safety and peace of mind of both patient and physician.

References


Unusual Presentation of Kaposi Sarcoma During Adalimumab Therapy: a Case Report

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Key words: psoriasis, biologics, kaposi sarcoma, TNF antagonist

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Introduction

Kaposi sarcoma (KS) is a rare angioproliferative malignancy associated with Human Herpesvirus-8 (HHV-8) that involves skin and visceral organs. It typically manifests with magenta-colored macules, papules, and nodules on the skin. Herein, we present a patient who developed pyogenic granuloma (PG)-like KS during adalimumab therapy for psoriatic arthritis.

Case presentation

A 48-year-old male applied to our dermatology outpatient clinic for a bleeding lesion on the right forth toe. The lesion occurred seven-months before and grew rapidly in last one-month. He has been diagnosed with psoriatic arthritis 4 years ago and treated with adalimumab, a tumor necrosis factor-α inhibitor (TNFi), for the last one year. Dermatological examination revealed a 1cm x1 cm diameter of reddish, ulcerated, protruding hemorrhagic nodule partially covered with hyperkeratotic crust and fibrin just under the fourth toe nail (Figure 1, A and B). Excisional biopsy was performed with provisional diagnoses of amelanotic malignant melanoma, PG and cutaneous squamous cell carcinoma. Histopathological examination showed nodular lesion in the dermis made up of atypical spindle shaped cells showing whorled structures and slit like spaces filled with erythrocytes. Immunohistochemical examination indicated HHV-8 positivity and confirmed the diagnosis of KS (Figure 1E). In detailed dermatological examination, purple-colored patches on the lateral aspects of both feet were noticed (Figure 1, C and D). HIV serology was negative. Adalimumab treatment was ceased immediately and the patient was addressed to oncology department for remaining lesions.

Conclusions

The potential of TNFis to increase the risk of malignancy including melanoma and non-melanoma skin cancer is still controversial. Although iatrogenic KS has been described in
Figure 1. (A, B) Reddish-purplish, firm, easy-bleeding nodule covered with hyperkeratotic crust and fibrin just under the right fourth toe nail. (C, D) Purple-colored patches on the lateral sides of both feet. (E) Spindle cells, slit-like spaces and erythrocytes, HHV8 positivity (inlet) are shown in histopathologic examination (H&E x200).
organ transplant recipients receiving immunosuppressive therapy, there are only a few reports of KS during TNFi therapy that were presenting as typically purplish-red patches and papulonodular lesions on the lower leg [1]. Classic KS is typically seen in older men (64–72 years) of Mediterranean, Eastern European (Ashkenazi) Jewish, or South American origin whereas endemic KS is limited to sub-Saharan Africa and is typically seen in young (25–40 years), black, HIV-negative men. On the other hand, KS and psoriasis speculated to share common pathogenesis particularly related with interleukin-6 cytokine pathway or the same human leukocyte antigen alleles. Although we cannot explain the exact mechanism of this association whether it is a co-existence of KS and psoriasis or it is triggered by adalimumab, HIV negativity and the early age of onset compared to classical KS suggested a relationship with adalimumab in the present case. Unlike reported KS cases induced by TNFi treatment, PG-like presentation with classical purple-colored patches was a remarkable finding of the current case. PG-like KS is a rare variant of KS that is difficult to diagnose clinically [2].

We present this rare case of PG-like KS that can be easily confused with other skin tumors in a patient under biologic treatment.

If characteristic purple-colored patches of KS on the lateral sides of feet were not overlooked on physical examination in the current case, it could have been possible to include KS in the clinical pre-diagnoses. Detailed whole body skin examination is crucial for dermatologists to provide correct clinical diagnosis for early management. Further evidence is needed to clarify the relationship between biologics and malignancy development.

References

Introduction

Endovascular interventional procedures are widely used for intracranial arterial pathologies treatment. They require realization of fluoroscopy, a technique that relies on X-rays to obtain real-time images [1]. Many cases of transient alopecia after this procedure have been reported.

Case Presentation

A 45-year-old male was admitted with an intracranial hemorrhage after a rupture of an aneurysm in the anterior communicating artery. Two embolization procedures were required. After 2 weeks, he experienced a partial hair loss, comprising the left temporoparietal scalp region. A 7.5-cm sized alopecia plaque with angular edges and rectangular morphology was observed (Figure 1). Pull test was positive. Trichoscopy showed black dots and short vellus hairs (Figure 2). Lack of peladic hairs ruled out alopecia areata. Skin biopsy revealed multiple pilosebaceous units with obliterated follicles without signs of fibrosis. After 2 months the patient showed complete hair regrowth without treatment.

Conclusions

Transient radiation alopecia (TRA) is an adverse effect, which usually appears with accumulated doses between 3-6 Gy. Greater doses than 6 Gy may cause scarring alopecia [1,2]. This is caused by the simultaneous entry of multiple follicular cells in catagen phase. The dose of radiation produced by a fluoroscopy unit is usually between 0.02-0.05 Gy/min.

Fifty-eight cases of TRA have been reported after intracranial arterial embolization, being more frequent in women, with a ratio of 1.41:1. The age varies from 13 years to 70 years, but most of the patients were between 30-50 years. Patients report sudden hair loss, producing plaques of alopecia whose size and shape vary depending on the model of the device used. The characteristic angular edges and the medical history are essential for the differential diagnosis with alopecia areata [1,2].
**Figure 1.** Alopecia area in the patient left temporoparietal region. Note the angular edges which give it a perfectly square contour.

**Figure 2.** Trichoscopy performed on the edge of the alopecia area. Black dots can be observed, as well as short vellus hair.
The cumulative radiation dose was in most cases greater than 3 Gy, with 92% of cases ranging between 3-6 Gy [1]. Only one case of scarring TRA has been reported [2]. In the case of our patient, we do not know the exact dose of radiation received, but a total dose greater than 3 Gy was estimated.

In trichoscopy, the most common findings include black dots and yellow dots, followed by short, vellus hairs. Broken hairs and white dots are less common [2]. These findings can be observed in alopecia areata. However, exclamation hairs are often seen in the latter, a finding that is not present in TRA.

Histological findings show anagen or catagen follicles lacking inflammatory infiltrate or scar tissue [2]. Differential diagnosis should be made mainly with alopecia areata, in which a peri- or intra-bulbar lymphocytic infiltrate with a “honey-comb” image is usually observed.

Time from the embolization procedure to the onset of alopecia ranges from 1-8 weeks. Most cases spontaneously resolve between 2-6 months, with complete regrowth. In some cases, cryotherapy, topical corticosteroids, topical minoxidil and/or intralesional triamcinolone were applied, without significant differences compared to untreated patients [2].

TRA is a transient condition that resolves without the need of treatment. Given the increase of such interventional procedures in recent years, it is important to know this entity and differentiate it mainly from alopecia areata. It should also be considered adding this side effect to the informed consent of such interventions.

References
Square-shaped Alopecia After Embolization of Intracranial Aneurysm: a Case Report and Review

Jorge Román-Sainz, Nicolás Silvestre-Torner, Fernando Gruber-Velasco, Belen Romero-Jiménez, Alejandro Lobato-Berezo, Adrián Imbernón-Moya
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P: Patients  AR: Age Range  M: Male  F: Female  ED: Estimated Dose  NS: Not Specified
A Case of Adult-onset Facial Cutaneous Mastocytoma: Clinical and Dermoscopic Findings

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Key words: solitary mastocytoma, adult, cutaneous mastocytoma, mastocytosis, facial


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Introduction

Cutaneous mastocytoma is a form of mastocytosis that usually affects newborns and children, representing an uncommon finding in adults [1]. Clinically, it presents with up to 3 yellowish, brown, or red nodular lesions mainly located on the trunk and extremities [1]. The most common dermoscopic feature is a yellow-orange blot pattern [1].

We report the unusual case of an adult-onset facial cutaneous mastocytoma, arising on the forehead, and describe a new dermoscopic pattern.

Case presentation

A 36-year-old woman came to our dermatology department for the presence of an asymptomatic erythematous plaque on the forehead, of two-month-duration (Figure 1). The patient was in good health and did not refer systemic symptoms; her medical and pharmacological history was unremarkable.

Dermoscopic evaluation revealed an irregular vascular pattern characterized by irregular linear vessels, some of which serpiginous, of steady caliber, on a pink-red background and perifollicular scar-like white areas (Figure 2). Incisional biopsy displayed the presence of a diffuse and homogeneous pan-dermal infiltrate of mast cells, with some perivascular and peri-adnexal lymphocytes and plasma cells in the upper dermis. To rule out systemic mastocytosis, routine blood tests as well as serum tryptase (sT) were performed resulting unremarkable. Based on clinical, dermoscopic and histologic findings along with normal sT levels and absence of systemic involvement, a diagnosis of cutaneous mastocytoma was made. The patient was started on topical tacrolimus with progressive subsiding of clinical manifestations.

Conclusions

Adult-onset cutaneous mastocytoma is a rare entity described in less than 20 patients so far [1]. Its diagnosis is
Figure 1. Clinical aspect of facial cutaneous mastocytoma: an erythematous plaque of the forehead.

Figure 2. Dermoscopy of facial cutaneous mastocytoma: irregular vascular pattern with linear vessels, some of which serpiginous, showing steady caliber; pink-red background; perifollicular scar-like white areas.
challenging as it may be confused with a vast spectrum of diseases according to its clinical presentation. Indeed, it may appear as a macule, papule, plaque or nodule and vary in color from yellow to brown, to red [2]. Dermoscopically, cutaneous mastocytoma has been reported to present a yellow-orange blot pattern [2]. Anyway, in our case, an irregular vascular pattern exclusively characterized by irregular linear and serpiginous vessels of steady caliber, on a pink-red background and perifollicular scar-like white areas were observed. More data are needed since reported dermoscopic descriptions are very scant. Given that the onset of cutaneous mastocytosis in adults is frequently associated with systemic disease, it has been recommended that the initial diagnostic work-up should include blood tests (complete blood cell count, serum chemistries with liver function tests, and sT levels), and also bone marrow biopsy (BMB) [2]. If there is no systemic involvement, all the above-mentioned investigations apart from BMB, should be repeated yearly [2]. In our case, due to the absence of systemic symptoms and normal sT, BMB was not performed. Concerning treatment, surgical excision is the most employed one, followed by topical or intralesional corticosteroids [2]; other treatments comprise pimecrolimus and pulsed dye laser therapy [2].

We reported the unusual case of adult-onset facial mastocytoma, arising on the forehead, and described new dermoscopic findings. Although the strength of our observation is limited by the single patient, we believe that enriching literature with new information may contribute to improve diagnosis of unusual manifestations.

Informed consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

References


Dermoscopic View of Papular Acantholytic Dyskeratosis of the Genitocrural Region

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¹Famagusta State Hospital Dermatology And Venerology Department, Famagusta, Cyprus
²Balıkesir State Hospital Dermatology And Venerology Department, Balıkesir, Turkey
³Famagusta State Hospital Pathology Department, Famagusta, Cyprus

Key words: acantholytic dyskeratosis, genital region, domed papules

Citation: Cebeci D, Can I, Kobat I. Dermoscopic view of papular Acantholytic Dyskeratosis (PAD) of the genitocrural region. Dermatol Pract Concept. 2022;12(3):e2022084. DOI: https://doi.org/10.5826/dpc.1203a84

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Introduction

Papular acantholytic dyskeratosis (PAD), also known as acantholytic dermatosis of the vulvocrural (or anogenital) region is a rare skin disorder reported more common in women than men. Recent studies have revealed that mutations in the ATP2C1 gene, typically seen in Hailey-Hailey disease, are also detected in papular acantholytic dermatosis of the anogenital region [1]. We report a case of a 49-year-old female with pruritic papular eruptions over the vulvocrural area. Histology of lesions revealed focal acantholysis with presence of dyskeratotic cells resembling corps ronds and grains.

Case Presentation

A 49-year-old female patient presented with persistent pruritic papular rash in both inguinal regions for 6 months. The patient applied to the obstetrics clinic with similar complaints and was referred to the dermatology clinic considering as condyloma. She had no history or family history of any skin disorder. Physical examination revealed multiple whitish pruritic papules with underlying erythematous patches in both inguinal regions (Figure 1A). No lesions were found at other locations and her nails were normal. KOH test was negative. Skin biopsy showed numerous typical acantholytic dyskeratotic cells in the stratum corneum and spinosum. There was also hyperkeratosis and irregular acanthosis in the epidermis and lymphocytic infiltration in the underlying dermis and no evidence of viral infection, dysplasia or malignancy (Figure 2). Dermoscopic examination (×10 magnification in polarized mode) showed an irregular star-shaped (circled) brown pigmentation and globular domed brown papules (Figure 1B). Direct immunofluorescence or genetic studies were not performed. Clinical and histopathological PAD was present. 0.1% topical mometasone furoate and topical tacrolin 0.1 cream were started on the patient. The patient showed a minimal improvement and is still being following up. Consent form was obtained from the patient.
Conclusions

Localized PAD to the genitocrural area is a rare and distinct clinical entity that was first described by Bernard Ackerman in 1972 as focal acantholytic dyskeratosis.

The dermoscopic features of Hailey-Hailey and Darier disease been described before in several studies but the dermoscopic features of the reported cases of PAD have not been experienced. In Hailey-Hailey disease, the combination of pink and white areas was more prominent. Minor erosions and ulcerations may also accompany it. In contrast, polygonal, star-like, roundish-oval, whitish, yellowish areas with peripheral halos have been described in Darier’s disease [2].

In this report, brown to gray hyperpigmented domed papules with a central hypopigmented core were the main dermoscopic findings. By reporting the dermoscopy of this case PAD, we would like to point out the usefulness of such dermoscopy in assisting the recognition of this entity.

References

Introduction

Human scabies is a worldwide skin infestation caused by the mite *Sarcoptes scabiei hominis* and remains a significant public health concern. The detection of the mite is essential for diagnosis and entodermoscopy strongly improves diagnostic reliability. The mite is visible on dermoscopy at the head of the burrow, due to its refractile area located between the buccal apparatus and the second pair of legs. This sign is called “triangle” sign or “delta glider” sign, or “hang glider” sign (Figure 1A, asterisk) [1]. The “triangle” sign is usually accompanied by reflecting bubbles along the tunnel called “jet trail” sign on wet dermoscopy (Figure 1A, arrow) [1]. Other less frequently observed dermoscopic signs have been described and one of the most recently described feature is the “gray-edge line” sign, that it’s due to the presence of mite feces containing melanin (Figure 1A, arrowhead) [1]. We present a new dermoscopic sign observed in 2 cases, in the era of progressive resistance of *Sarcoptes scabiei hominis* to standard treatments.

Figure 1. (A) Dermoscopy of a scabies burrow showing the “delta glider” sign (asterisk), reflective bubbles within the burrow referred to as “jet trail” sign (arrow) and blackish-gray lines at some points of the burrow walls consistent to the “gray-edge line” sign (arrowhead). (B) Microscopic examination of a Sarcoptes scabiei hominis with classical features: the gut area appears poorly demarcated and of the same color of the adjacent structures (arrow).
Case presentation

We observed 2 cases of young patients (a 10-year-old male and a 5-year-old male) referred to the dermatologic unit for scabies present for several months, treated with multiple cycles of permethrin 5% cream. Physical examination revealed persistent multiple mite burrows with classic dermoscopic image of “delta glider” sign (Figure 2, A-C, asterisk), corresponding to the anterior part of the mite (Figure 2, B-D, asterisk), associated with a new dermoscopic sign, which we called the “butterfly” sign, characterized by a butterfly-shaped reddish area just below the “delta glider” sign (Figure 2, A-C, arrow). The microscopic examination of the scraped skin in correspondence to the burrow showed in both patients the presence of the mite with a well-defined butterfly-shaped gut area, with a reddish coloration resembling blood (Figure 2, B-D, arrow). Of note, the gut area of the Sarcoptes scabiei hominis mite is usually not so clearly visible under the microscope (Figure 1B, arrow).

Conclusions

Recently, several authors described the emerging phenomenon of resistance of mites to standard treatments, in particular...
to permethrin, as in our cases [2]. Considering these recent evidences, this report suggests a new dermoscopic sign as a possible marker of *Sarcoptes scabiei hominis* evolution.

**References**


Do PD-1/PDL-1 Inhibitors Play a Triggering or Causative Role in the Development of Paraneoplastic Dermatomyositis?

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Key words: PD-1 inhibitors, dermatomyositis, paraneoplastic, breast cancer, immune-related adverse events
Citation: Starace M, Pampaloni F, Carpanese MA, et al. Do PD-1/PDL-1 Inhibitors Play a Triggering or Causative Role in the Development of Paraneoplastic Dermatomyositis? Dermatol Pract Concept. 2022;12(3):e2022105. DOI: https://doi.org/10.5826/dpc.1203a105
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Introduction
The use of immune checkpoint inhibitors therapy in cancers is widely diffuse but the dermatologic immune-related adverse events (irAEs) are not completely characterized. We present the first case of paraneoplastic dermatomyositis triggered by atezolizumab.

Case presentation
A 53-year-old woman affected by ductal infiltrative breast cancer underwent mastectomy and lymphadenectomy, followed adjuvant chemotherapy. Later she started paclitaxel weekly and atezolizumab after 2 months. At the fifth infusion of atezolizumab she developed a skin rash attributed to drug. Dermatologic examination revealed marked butterfly-facial edema with periocular swelling, erythematous-violaceous plaques of the face, upper chest and back. (Figure 1A). Erythematous papules coalescing into plaques of the metacarpophalangeal and proximal interphalangeal joints were detected (Figure 1B). Hemorrhagic onycholysis and periungual erythema were detected by capillaroscopy that revealed capillary loss, tortuosity, ramified, enlarged capillaries, and microhemorrhages (Figure 1C and D). A skin biopsy from a papule of the back of the hand showed an interface dermatitis and focal mucin deposition in the dermis. Laboratory testing revealed positive ANA (1:320), normal CPK (212 U/l), mild increased serum aldolase (15.5 U/l), normal transaminases. Given the clinical presentation, capillaroscopy, histopathology and ANA positivity...
Conclusions

PD-1/PDL-1 inhibitor immunotherapy represents a successful treatment for advanced malignancies; it can be associated with lots of irAEs, among which dermatomyositis. Guidelines recommend temporary or permanent drug

we made the diagnosis of dermatomyositis. Between myositis-specific antibodies requested anti-TIF y antibodies were significantly positive (negative anti-Ro and anti-JO). Systemic prednisone 50 mg daily and intravenous immunoglobulins were prescribed with improvement of the clinical signs (Figure 2).

Figure 1. (A) Facial butterfly-edema, with periocular swelling, erythematous-to-slightly-violaceous plaques sparing the frontal region and the submental area. (B) Erythematous discrete papules coalescing into plaques of the metacarpophalangeal and proximal interphalangeal joints. (C) Capillaroscopic examination: capillary loss, tortuosity, ramified, enlarged and giant capillaries, and microhemorrhages 50X magnification. (D) 70X magnification

Figure 2. The same patient after the therapy with intravenous immunoglobulin: evident improvement on face (A) and hands (B).
This case adds new findings to the literature regarding dermatomyositis associated with PD-1/PDL-1 inhibitors. PD-1/PDL-1 inhibitors could have a triggering role rather than a causative role in the development of dermatomyositis. Clinicians should be aware that facing a patient affected by metastatic cancer treated with PD-1/PDL-1 inhibitors, cutaneous adverse events such dermatomyositis may be not related to the treatment but also to the underlying disease, preventing the interruption of safety treatments.

References

Calcinosis Cutis in Association With Long-term Stasis After Electrical Burn Injury: a Case Report

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Keywords: calcinosis cutis, dermoscopy, dystrophic calcification, leg ulcer

Introduction
Calcinosis cutis is an uncommon disorder caused by an abnormal deposit of calcium phosphate in the skin [1].

Case Presentation
A 55-year-old male patient with a long-lasting wound on the left ankle presented with complaints of swelling and itching on his left ankle. According to his medical history, he had an electric shock to the left leg 33 years before and the wound was closed with grafting. Ulceration developed at the same site 2 years before he presented at our clinic.

On physical examination, he had an erythematous, ulcerated, sclerotic, 20 cm x 15 cm in size wound over the left lateral malleolus. On this wound, there were three fluctuating masses with overlying intact skin which were 1 x 1.5, 1 x 2 and 3x3 cm in size, respectively (Figure 1A). Dermoscopic examination showed blue to gray structureless areas, numerous coiled vessels with patchy distribution and scales (Figure 2A). A thick, profuse, white, chalky material was discharged from the hole created via a punch biopsy (Figure 1B).

Histopathological examination revealed hyperkeratosis, acanthosis, superficial dermal vascular proliferation along with dermal and subcutaneous calcification foci. X-ray examination showed irregular-defined calcified foci over the posterior aspect of the distal end of the fibula extending in a linear fashion (Figure 2B). Arterial and venous Doppler ultrasound examinations revealed normal findings.

Biochemical parameters including liver and renal function tests, alkaline phosphatase, serum calcium, phosphorus, sodium, potassium, vitamin D levels, parathyroid hormone levels, CEA, AFP, CA-15-3, CA-19-9, total PSA were within normal limits.

The patient was diagnosed with a stasis ulcer with dystrophic calcification and was managed with extremity elevation, wound dressing and oral diltiazem. The patient, who has been under our control for 18 months, has not had a recurrence of the fluctuating mass (Figure 1C).
Figure 1. (A) An erythematous, ulcerated, sclerotic wound over the left lateral malleolus and three fluctuant masses. (B) A thick, profuse, white, chalky material discharged from the hole created via a punch biopsy. (C) 18 months after the treatment, it is seen that the fluctuant masses still do not recur.

Figure 2. (A) Dermoscopic appearance: blue to gray structureless areas, numerous coiled vessels with patchy distribution and scale. (B) X-ray of the left lower leg showing irregular-defined calcified foci over the posterior aspect of the distal end of the fibula extending in a linear fashion.

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

Conclusions

Cutaneous calcification has been divided into five major types according to etiology: dystrophic calcinosis is the most common type of calcinosis that is associated with infection, inflammatory processes, cutaneous neoplasm, or connective tissue diseases. Other types of calcinosis cutis are metastatic calcification, idiopathic calcinosis cutis, iatrogenic, and mixed calcinosis [1,2].

In the literature there a few studies on dystrophic calcification due to stasis developed as a result of chronic venous insufficiency [1]. Arterial and venous Doppler results of our patient were normal. However, the stasis might have been caused by worsened lymphatic drainage due to previous operations and tissue damage experienced by the patient.

Dystrophic calcification is reported to be a rare cause of non-healing leg ulceration [2]. It should be kept in mind that dystrophic calcification of the skin may also be associated with persistent ulceration in the setting of stasis.

The treatment of calcinosis cutis is not well-established. Apremilast, diltiazem, bisphosphonates, probenecid, aluminum hydroxide, aimed at altering the serum calcium-phosphorus
levels, have been tried. Long-term treatment with diltiazem was reported to decrease the size of calcium deposits. Surgical excision or curettage is appropriate in selected patients [2].

References


Cutaneous Spitzoid Melanoma in Childhood After Acute Lymphocytic Leukemia

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Keywords: melanoma, Acute Lymphocytic Leukemia, Spitz Nevus, Skin Cancer

Introduction

Acute lymphocytic leukemia (ALL) is the most common childhood malignancy. It has a good prognosis but one-third of all childhood ALL deaths are due to toxicity or secondary malignancies. We report the case of a patient with a personal history of ALL who had cutaneous spitzoid melanoma at the beginning of puberty.

Case presentation

A 13-year-old female patient from São Paulo, Brazil, presented, in 2015, a well-defined, erythematous, ulcerated brown nodule in the left temporal region, with a 1-year evolution (Figure 1A). She presents a personal history of ALL diagnosed in 2013, treated with chemotherapy. Dermoscopy shows polymorphic vessels, exulceration, hematic crusts, and chrysalis (Figure 1B). No specific finding of the melanocytic lesion was present.

The initial hypotheses were keratinocytic or vascular neoplasms being performed incisional biopsy for diagnosis. A histopathological analysis showed a neoplasm with cells arranged in nests, ample and eosinophilic cytoplasm, with oval or rounded nuclei and prominent nucleoli, whose diagnosis was infiltration by primary melanoma. Excisional biopsy confirmed the diagnosis of nodular, ulcerated, spitzoid, Clark V melanoma with tumor thickness (Breslow) of 4.7 mm (Figures 2). Surgical treatment with wide excision was performed, followed by adjuvant treatment with interferon alpha 2b at a dose of 6350,000 IU, subcutaneously, 3 times a week for 2 years, the only adjuvant treatment available at the time of diagnosis. The patient remained in oncological follow-up for 5 years and in remission of both neoplasms.

Conclusions

This case report shows a remarkable clinical similarity with what was reported by Goldes et al. in 1984, whose initial
diagnosis, however, was Spitz nevus, but the patient died of metastatic melanoma [1]. The differential diagnosis between spitz nevus in its atypical presentation, such as aggressive spitz tumor of undetermined biological significance, and spitzoid melanoma is a major challenge [2]. Both may share findings such as fusiform melanocytes, prominent nucleoli, junctional nests, diameter greater than 10 mm, and high-grade nuclear atypia. The characteristics that favor the diagnosis of melanoma are greater depth of the lesion, involvement of reticular and subcutaneous dermis, mitosis in the deep dermis, nuclear and cellular pleomorphism, asymmetry and ill-defined limits, all of them present in our report. Nevertheless, in certain situations only the development of metastasis will define the diagnosis. We can assume that the approach presented in the face of the diagnosis of spitzoid melanoma (wide excision and adjuvant immunotherapy) may have influenced the outcome of the present report. The most common secondary malignant neoplasms after ALL are lymphoreticular (acute myelocytic leukemia and Hodgkin disease), followed by endocrine, keratinocytic, and renal tumors. Immunosuppression by chemotherapy and radiotherapy is related to an increased risk of developing a subsequent neoplasm but not necessarily related to their causes. In addition to being rare in childhood, the occurrence of cutaneous melanoma as a secondary neoplasm after ALL, is even more uncommon, and this case in our knowledge is the second case reported in the literature. However, it should be considered mainly in the presence of a pigmented nodule on the face.

References

Clinical, Dermoscopic and Radiological Features of Heel Stick Calcinosis Cutis

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Key words: calcinosis cutis, dystrophic calcification, dermoscopy, heel-stick injury

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Introduction

Heel-stick calcinosis is a common disorder of infants due to heel prick injury. Although the condition is benign and self-resolving, it may cause anxiety and concern to the parents. Dermoscopy allows non-invasive confirmation of the diagnosis and differentiates other disorders with similar morphology thus helping in reassuring the parents.

Case report

An 8-month-old male was brought to us with multiple whitish lesions on the soles of both the feet since the past 4 months. On enquiry, parents revealed multiple heel pricks done for blood tests in the past. Examination revealed multiple discrete porcelain-white papules and carateriform keratotic papules (Figure 1A). Polarized dermoscopy using handyscope (FotoFinder® systems GmbH) revealed 2 types of lesions - homogenous circumscribed white clods and keratotic lesions showing central amorphous yellow and white clods surrounded by thick concentric scales (Figure 1B). A diagnosis of calcinosis cutis secondary to heel stick injury was made. Plain X-ray revealed multiple white opacities within the soft tissues of the heels (Figure 1C). One of the lesions was punctured and chalky white material was expressed out which was dissolved by hydrochloric acid suggesting that it was calcium hydroxyapatite (Figure 2, A-C). Laboratory tests for calcium, phosphorous and vitamin D were all normal. A final diagnosis of dystrophic calcinosis cutis following heel-stick injury was hence established. As the condition is self-limiting, the parents were reassured about the same.

Conclusions

Heel-stick calcinosis is a form of dystrophic calcification following heel pricks. Multiple pricks account for majority of the cases although cases following single prick have also been described. Release of alkaline phosphate by injured tissue elevates the local pH favoring calcium deposition. The lesions can be solitary, or multiple discrete yellow-white papules or nodules and keratotic lesions which may be seen extruding through the epidermis. The lesions usually regress within about 2-3 years of age [1].
Dermoscopy of calcinosis cutis exhibits homogenous white areas as described above. The dermoscopy of keratotic lesions as described above highlights the process of trans-epidermal elimination of calcium deposits. Warts, callosities and corns can present as keratotic papules on the soles. Dermoscopically they show compact keratin, and the warts in addition show red or black dots surrounded by white halo. These lesions are rare in infants and do not show white homogenous material. Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) presents with keratotic papules with collarette typically involving palms and soles and presenting at birth or in early childhood. The lesions are grouped and frequently along the Blaschko lines. Dermoscopy of PEODDN on palmar skin showing keratin filled pits has been described [2]. Hence, discrete lesions and presence of amorphous white substance centrally differentiates heel-stick calcinosis from PEODDN. Finally, milia-like calcinosis cutis exhibits similar dermoscopic features as described above. It is mostly associated with Down syndrome characterized by discrete white papules involving hands and feet.

Although a fairly well-known entity and the diagnosis essentially clinical, application of dermoscopy in the diagnosis of heel stick calcinosis provides further support and refutes the need for biopsy and/or radiological imaging.

References


Figure 1. Dermoscopy: polarized, x20. (A) Multiple discrete white and keratotic papules on the heels. (B) Dermoscopy shows well-defined homogenous white dots (black arrows) and keratotic lesions with central yellow and white amorphous cloids surrounded by concentric thick scales (blue arrows). (C) Plain X-ray shows circumscribed opaque densities along the margins of the heel.

Figure 2. (A) Chalky-white material expressed out of a papule. (B) Material as observed under light microscope. (C) Complete dissolution of the material was seen on treatment with hydrochloric acid.
A Pink Nodule With White Halo: Dermoscopy of Halo Melanoma

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Introduction

Halo phenomenon consists in an area of depigmentation around a skin lesion. It represents a benign regression phenomenon most associated with acquired nevi [1]. Very rarely, a hypopigmented halo can also occur around melanomas (halo melanoma, HM). Dermoscopy may help to distinguish them from common halo nevi (HN).

Case presentation

We report the case of a 63-year-old man with a nodular, amelanotic lesion on the back surrounded by an achromic halo. The patient reported that the lesion occurred 1 year before, with a progressive increase in size during the last 5 months. The lesion had become itchy, developing a vitiligo-like halo. Physical examination showed a symmetrical, reddish nodule, 8 mm in diameter, surrounded by a whitish area of about 2.5 cm x 2 cm. No other areas of depigmentation were detected on total body examination (Figure 1, A and B). Dermoscopy revealed central whitish and blue areas on a homogeneous pink-red background and polymorphous vascular pattern characterized by arborizing, hairpin and linear irregular vessels, mainly arranged at the periphery. No pigment network was detected (Figure 1, C and D). Histology showed achromatic atypical melanocytes aggregated in the dermis, without epidermotropism (Figure 2A). A perilesional lymphocytic infiltration with fibrosis at the periphery of the nodule was observed. Immunohistochemical analysis was positive for melanocytic markers but did not show basal melanocytes in the area of epidermidis surrounding the nodule (Figure 2B). Total-body positron emission tomography scan results were unremarkable. The diagnosis of dermal melanoma was finally made (Breslow thickness 2.4 mm, non-ulcerated). Wider local excision and sentinel node biopsies were negative. The patient was disease free at 12 months follow-up.
Figure 1. (A) Clinical overview of the patient. (B) Naked-eye appearance of amelanotic halo melanoma as a reddish papule surrounded by an achromic halo. (C) Dermoscopy showed central whitish and blue areas on a homogeneous pink-red background and polymorphous vascular pattern. (D) Close-up of dermoscopic view.

Figure 2. (A) Dermal proliferation of atypical achromic melanocytes with nodular dermal expansion and collarette formation at the periphery (H&E, 4x). (B) Immunohistochemistry supports the melanocytic phenotype and emphasizes the lack of junctional melanocytes in the epidermis straddling the collarette (HMB45 immunostaining with hematoxylin counterstain, 4x).

Conclusions

HN occurs in about 1% of the general population while HM is rarer, with only few cases reported in literature [1]. Both HN and HM appear as a melanocytic lesion surrounded by a rim of white halo. The main distinguishing clinical feature is that the shape of the achromic halo tends to be more asymmetric in HM compared to HN [1]. HM also
seems to occur at older age. There are only a few reports dealing with dermoscopy of HM, characterized by melanoma-specific multicomponent patterns with atypical pigmented network, irregular dots/globules, streaks, blotches, blue-white veil and atypical vascular structures [2]. In our patient the absence of the pigmentary network and the polymorphous vessels in asymmetric arrangement did not allow to rule out cutaneous melanoma metastasis, even if hypopigmented peripheral halo has been very rarely reported in such cases [1]. Histology did not highlight primary melanoma criteria, as ulceration, intraepidermal component, presence of associated nevus or regression. However, the absence of primitive melanoma in another site, as revealed by instrumental exams, led us to conclude for the diagnosis of primary dermal melanoma with peritumoral achromic halo.

HM is the most worrisome differential diagnosis of HN. In most cases, dermoscopy may provide useful additional information to clinical assessment, especially about the vascular pattern. However surgical excision and histopathological examination are mandatory especially in case of achromic nodular lesion like in our patient.

References


Agminated Nevi of the Foot with Checkerboard and Blaschkoid Distribution

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Introduction

Agminated nevi (AN) are an infrequent group of melanocytic nevi (MN), whose name derives from the Latin word agmen, meaning “aggregation.” AN are indeed a clustered group of lesions confined to a localized area of the body. Many pigmented lesions have been described in the literature as agminated, including Spitz nevi, blue nevi, lentigines, congenital melanocytic nevi (CMN), acquired melanocytic nevi (AMN). We report a case of a woman with AN of the foot with a peculiar checkerboard and blaschkoid distribution.

Case presentation

A 34-years-old woman was seen for multiple MN arranged in a checkerboard pattern on her right foot. She reported that some nevi have been present on the sole since infancy, while many other nevi appeared on the lateral, medial and plantar location later on. Dermoscopically, the pigmented lesions of the lateral margin of the foot (Figure 1A), as well as those located on the fourth and fifth toe and in fourth interdigital space (Figure 1B) showed a reticular pattern (Figure 1D) and a transition pattern (reticular plus parallel furrow or lattice-like) (Figure 1E). The nevi located on the sole (Figure 1C) disclosed various dermoscopic patterns: homogeneous, Figure 1F), fibrillary (Figure 1G), lattice-like pattern (Figure 1H), lattice-like pattern with ovoid structure of the furrows (Figure 1I).

According to the patient medical history and dermoscopic patterns of acral nevi, a diagnosis of uncommon coexistence of acral CMN and AMN was done. Unfortunately, the patient refused the biopsy and histopathologic examination of some nevi. Anyhow, we decided to plan clinical and dermoscopic monitoring of our patient every 3–6 months.
Besides, we know from the literature that common and dysplastic AMN can be arranged seldom in a checkerboard pattern, while CMN are commonly arranged along the Blaschko lines [1]. Briefly, the checkerboard pattern of acral AMN has been explained by an early postzygotic mutational event giving rise to loss of heterozygosity, that is the loss of a normal wild-type allele, and which leads to the expression of a mutant or recessive allele [2].

Although the diagnosis was not confirmed by a biopsy, this is a case with a peculiar arrangement of AN involving the acral area.

Conclusions

According to the dual concept of nevogenesis, small CMN are present at birth or in the first years of life (so-called tardive small CMN) and are clinically and dermoscopically indistinguishable from early-onset AMN. They are both genetically determined, usually share the same dermoscopic features (ie globular pattern) and evolve in nevi with a cobblestone or homogeneous pattern in adult life. These nevi often exhibit overlapping clinical and histopathological features. On the contrary, the “true” AMN develops in adolescence and adult life and could be influenced by environmental factors, such as an intermittent sun exposure.

In our patient, the lesions with a homogeneous brown-grayish or a parallel-furrow pattern combining with an ovoid shape of the lines, mainly located on the sole along Blaschko lines, and appeared in infancy, could be CMN. On the contrary, the lesions with a reticular and checkerboard pattern, on lateral, medial and interdigital sides of the foot, appeared in late childhood and adolescence, could be AMN.

Besides, we know from the literature that common and dysplastic AMN can be arranged seldom in a checkerboard pattern, while CMN are commonly arranged along the Blaschko lines [1]. Briefly, the checkerboard pattern of acral AMN has been explained by an early postzygotic mutational event giving rise to loss of heterozygosity, that is the loss of a normal wild-type allele, and which leads to the expression of a mutant or recessive allele [2].

Although the diagnosis was not confirmed by a biopsy, this is a case with a peculiar arrangement of AN involving the acral area.

Reference

Dermoscopy Performs an Important Role to Diagnose Radiation-induced Angiosarcoma on the Breast

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Introduction

Radiation-induced angiosarcoma (RIAS) is a rare subtype of angiosarcoma that originates from endothelial cells exposed to radiation. The breast is the most common location of this condition, and the incidence of RIAS on women treated with breast-conserving surgery and radiotherapy vary from 0.14% to 0.5%, depending upon the study. Prognosis is poor, recurrences are common, distant metastasis may occur, and 5-year survival rates are between 28%-54% [1].

On early stages it usually presents itself as painless blue-red patches on a previously irradiated skin area, that progresses to red or violaceus plaques and eventually irregular borders with a nodular appearance. Differential diagnosis includes hematomas, hemangiomas, cellulitis, radiodermatitis or atypical vessel lesions. Biopsy is the most accurate method for the diagnosis.

This is a case report of RIAS on the breast, with relevant clinical and dermoscopic features.

Case Presentation

A 68-year-old Caucasian woman presented with a 3 cm, asymptomatic violaceus plaque on the areola of her right breast (Figure 1A), 8 years after radiotherapy for the treatment of an invasive ductal carcinoma on the same location. Dermoscopy showed a central hemorrhagic crust, surrounded by a purple background, with blue-red globules and shiny-white structures (Figure 1B). Histopathological examination with the presence of spindle cells proliferation, forming bundles and compact nodules in the dermis, alongside positive immunohistochemistry for Ki-67 and CD34 markers, confirmed well-differentiated angiosarcoma (Figure 2).

Conclusions

Diagnostic of incipient radiation-induced angiosarcoma is difficult due to the ample differential diagnosis and non-specific characteristics of this neoplasm. Although none
Figure 1. (A) Clinical photo showing a violaceous plaque, with irregular borders on the areola. (B) Dermoscopy (DermLite DL4, x10) with purple background, red globules, hemorrhagic crust and shiny white structures.

Figure 2. (A) Histopathological features showing proliferation of spindle cells, arranged in a lobular pattern on the dermis and extravasated red blood cells (H&E, x10). (B) Spindle cells pleomorphism and cellular atypia (H&E, x40). Immunohistochemical staining with positive CD34 marker (C) and Ki-67 marker (D) on the tumor cells, confirming its endothelial origin and high proliferation activity, respectively.
are pathognomonic of RIAS, dermoscopic patterns are important to establish the vascular origin of the lesion, and can help in the differential diagnosis with other vascular tumors that already have dermoscopic features known as angiokeratoma and Kaposi sarcoma [2].

In the present case, dermoscopic findings corroborate those of past reviews, such as variable red, blue or purple structureless areas, white lines and globules most visible on the periphery, reaffirming these as important characteristics in the diagnostic of RIAS [3].

In conclusion, the clinical history of previous radiation therapy associated with dermoscopic findings provides a high suspicion of RIAS, which means that incisional biopsy should be performed early for the correct diagnosis and rapid treatment.

References

Dermoscopy of Pseudoepitheliomatous Hyperplasia Tattoo Reaction Pattern

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Keywords: dermoscopy, pseudoepitheliomatous hyperplasia, squamous cell carcinoma, tattoo

Introduction

Delayed cutaneous tattoo reactions are a relatively rare occurrence and include, lichenoid, granulomatous, allergic, pseudoepitheliomatous (PEH), and pseudolymphoma. Dermoscopic features of delayed tattoo reaction patterns are rarely reported [1].

Case presentation

A 21-year-old male had a one-year history of a slow-growing, asymptomatic lesion over a blue tattoo. It started six months after the tattooing. Cutaneous examination showed solitary erythematous to bluish verrucous plaque over the tattoo (Figure 1A). Dermoscopic examination under non-polarized mode revealed two distinct zones. The central area had white scales, white to pinkish-white structureless area, comedo-like opening with keratotic plugging, white circles, red globules, hemorrhage, hairpin, and linear irregular vessels. The peripheral zone showed a gray-white to bluish-white structureless area (Figure 1, B and C). The differential diagnoses included were lupus vulgaris, tuberculosis verrucosa cutis (TBVC), chromoblastomycosis, and granulomatous tattoo reaction pattern. Histology showed hyperkeratosis, parakeratosis, pseudoepitheliomatous hyperplasia, spongiosis, and lymphocytic exocytosis. In addition to tattoo pigment, the dermis had a subepidermal band-like, perivascular and peri-adnexal predominant lymphocytic infiltration and occasional plasma cells. Also, the epidermis showed focal keratinocyte swelling, dyskeratotic cells, and the dermis showed an increased number and dilated dermal blood vessels. (Figure 2, A and B). Other investigations were within normal limits. The diagnosis of PEH tattoo reaction pattern was made, and the patient was treated with intralesional triamcinolone acetonide 40 mg/ml.

PEH is the result of benign hyperplasia of the epidermal and adnexal epithelium. Tattoo-induced PEH is a rare
benign reaction pattern commonly to red or purple pigment. Differentiating PEH from squamous cell carcinoma (SCC) is vital to reduce patient morbidity and cosmetic disfigurement, as the latter can occur independently over a tattoo or arise from the PEH. The early onset and lesions confinement to the tattoo margins favors PEH, while a late onset and involvement beyond the tattoo border suggest SCC.
A homogenous violaceous pattern with follicular white-yellow halo was reported in a case of tattoo pseudolymphoma [1]. The dermoscopic features described for SCC are scales, keratin, white circles around a dilated and plugged follicular infundibulum, white structureless area, blood spots, and hairpin, linear, linear irregular, glomerular, or polymorphic vascular pattern [2]. In the index case, the following dermoscopic features overlapped with SCC: white homogenous area, keratotic follicular plugging surrounded by white circles, and polymorphous vascular structures. However, the patient age, temporal correlation, and circumference of the plaque, along with dermoscopic findings, were suggestive of PEH.

The dermoscopic features described for other differential diagnoses are the following: lupus vulgaris shows a diffuse or localized yellow-orange structureless area and linear branching vessels; TBVC displays a yellowish-red to yellowish-brown areas, scales, and out-of-focus vascular structures; chromoblastomycosis is reported to have scale, crust, and yellow structureless and pink-white areas; and granulomatous tattoo reaction shows crystalline structures and orange structureless area [3-5].

Conclusions

We are reporting the clinico-dermoscopic-pathologic features of a case of PEH tattoo reaction pattern. Dermoscopy may help distinguish PEH from other differential diagnoses described above, but not from SCC, in which case only clinical and anamnestic data may help in their differentiation.

References

Lymphoma Developing in a Patient With Long-term Antitumor Necrosis Factor Therapy

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Key words: lymphoma, antiTNF, adalimumab, psoriasis

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Introduction

Some studies have shown that tumor necrosis factor (TNF) alfa inhibitor therapy may increase the risk of lymphomas [1]. It is historically known that psoriasis can also increase the risk of cutaneous lymphomas. Here we present a case of a primary cutaneous anaplastic large cell lymphoma in a patient under treatment with adalimumab for psoriasis and psoriatic arthritis.

Case Presentation

Patient presented to the clinic with a shallow one-month ulcerative lesion, with infiltrated borders on the buttock. The patient had been on adalimumab for, approximately, the last 10 years due to psoriasis and psoriatic arthritis (Figure 1). A biopsy was performed for histopathology and immunohistochemistry analysis. The report showed cohesive sheets of large CD30-positive anaplastic cells confirming the

Figure 1. Ulcer on the buttock.
diagnosis of CD30+ anaplastic T-cell lymphoma. Staging determined a cutaneous primary lymphoma with no other organs involved. The patient is currently under treatment for the disease (Figure 2).

Conclusions

Studies have shown that the most common lymphoma subtype associated with anti-TNF therapy is non-Hodgkin B-cell lymphoma [1]. In the other hand, it is known that psoriasis itself can increase the risk of cutaneous lymphoma. In this case, T-cell lymphoma is the most associated lymphoma subtype, mainly mycosis fungoides. Our patient presented a primary cutaneous anaplastic large cell lymphoma. This subtype of cutaneous T-cell lymphoma usually presents as a solitary nodule that often develops ulceration, as presented in this case. The prognosis is usually favorable with extracutaneous dissemination occurring in approximately 10% of the patients. Radiotherapy is usually the initial choice of treatment, but chemotherapy could also be considered. More recently, a study by Langley et al stated that longer-term (≥ 12 months) treatment with a TNF alpha inhibitor, but not shorter-term treatment, was associated with increased risk for malignancy [2]. The patient presented here had been under treatment for, approximately, 10 years.

In conclusion, studies are controversial regarding if there is an increased risk of malignancy due to anti-TNF alpha therapy, with a tendency of relating it to the duration of the treatment. We presented a case of a patient with a long-term treatment with adalimumab for psoriasis and psoriatic arthritis who developed a cutaneous lymphoma. Further studies are needed to determine the risk of lymphomas in patients with long term anti-TNF therapy, but physicians should remain aware of this possibility when following patients under this treatment.

References

Eccrine Porocarcinoma Arising From an Eccrine Poroma: a Case Report

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Introduction

Eccrine porocarcinoma (EPC) is the malignant counterpart of eccrine poroma (EP) and is mostly found on the lower extremities in elderly adults [1]. EPC may develop as a primary tumor or from a benign long-standing EP with malignant transformation. Dermoscopy is used increasingly to facilitate clinical diagnosis [2]. In this report, we describe a case of an invasive EPC originating in an eccrine poroma and associated with an adjacent satellite lesion of eccrine poroma.

Case Presentation

A 68-year-old woman referred a vegetative lesion in the right plantar region with one year of evolution. She reports that the lesion appeared after local trauma caused by sandals and complains of pain. On physical examination, it presented as an ulcerated, vegetative, bulky exophytic tumor associated with a satellite small plaque (Figure 1A). Dermoscopy of the lesion showed predominantly round-to-oval shaped pink white structureless areas surrounded by white-to-pink halo and polymorphous vessels including coiled and branched vessels with rounded ending (flower-like vessels) (Figure 1B). Ulcerated areas presented polymorphous vascular pattern with linear irregular and dotted vessels with splinter hemorrhage (Figure 1C). Histopathology showed that the main lesion was compatible with ulcerated porocarcinoma, in association with an eccrine poroma, invading the inferior reticular dermis, without vascular and perineural invasion (Figure 2, A and B). The satellite lesion was diagnosed as eccrine poroma. There were no signs of postoperative recurrence or metastasis after 6 months of follow-up.

Conclusions

EP is a benign tumor of the sweat gland that arises from acrosyringium. EPC is a rare malignant skin tumor that usually appears in the lower limbs of elderly people as nodule, plaque or papule pink to red, sometimes with ulceration [1]. EPC may arise de novo or can originate from malignant transformation of an EP [2]. An EP that shows changes, as sudden growth, ulceration and spontaneous bleeding turns...
on the red flag for an arising EPC. In our case the patient had both tumors, EP and EPC, and it seems probable that the EPC originated from the EP.

According to previously reported, dermoscopic features may overlap between EPC and EP, such as pink white structureless areas and white-to-pink halo, although in EPC they are present focally in the tumor and do not comprise the entirety of nodules, such as in EP [1]. Vascular pattern is often polymorphous in EPC, usually combining hairpin, dotted and linear irregular vessels, while coiled, glomerular and the typical flower, leaf-like vessels are less frequently found [1]. In the histopathological examination the usual findings include nuclear atypia, increased mitotic activity rate and necrosis. In the clinical examination, infiltrated borders, bleeding, growth and ulceration are important features that may indicate malignancy in EP-like lesions [2].

Since EPC shares multiple features with other tumors and is a rare skin neoplasm, diagnosis is a challenge. Anatomopathological signs of invasion and cellular pleomorphism in an eccrine tumor are clues to the definitive diagnosis [2]. Treatment is necessary due to the aggressive nature of the tumor, and surgery is the first option.

References


Dermoscopy of Cutaneous Neurocristic Hamartoma and Report of its Rare Clinical Presentation

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Keywords: dermoscopy, cuticis verticis gyrata, neurocristic hamartoma, Blue Naevi

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Introduction

Cutaneous neurocristic hamartoma (NCH) is a rare hamartomatous proliferation of melanocytic, neuroid, and mesenchymal tissues first described by Tuthill et al in 1982 [1].

Case Presentation

A 33-year-old man presented with swelling of the scalp and multiple bluish swellings on the body since birth. He had a surgical excision of a scalp lesion at four years of age after which the swelling had recurred. There was a gradual increase in size of the swelling since the past four years. On examination, he had a cerebriform swelling with alopecia, akin to cuticis verticis gyrata with areas of bluish color and depigmentation seen over the occipital scalp and extending onto the neck. (Figure 1A). Multiple bluish firm nodules were seen over the trunk (Figure 1B). The skin lesions on dermoscopy (FotoFinder Systems GmbH) showed varying colors from blue, gray, white and brown color. The dermoscopy of nodules showed blue clods over a gray background with peripheral brown pigment network (Figure 1C), blue gray clods on a white background (Figure 1D) blue clods on a white background with brown dots (Figure 1E). The scalp nodule showed blue gray clods, white featureless areas, brown dots and streaks, multiple clustered dotted and linear vessels (Figure 2A). The clinical differential diagnoses considered were blue nevus, cerebriform intradermal nevi, nevus sebaceous and cylindroma. An excision biopsy and split thickness skin grafting of the scalp lesion was done. Histopathology from the scalp and trunk nodule showed proliferated spindle to epithelioid nevus cells in dermis and intervening stroma showing a proliferation of bland spindle shaped cells, few of which had wavy nuclear contour (Figure 2, B and C). On immunohistochemistry, the nevus cells were positive for S100, HMB 45 and Melan A and stromal spindle cells for CD 34 (Figure 2, D and E). The MIB index was less than 1%. A diagnosis of benign NCH was made.
Figure 1. (A) Cerebriform swelling with alopecia, akin to cutis verticis gyrata with areas of bluish color and depigmentation seen over the occipital scalp. (B) Multiple bluish firm nodules over the back. (C) Dermoscopy of skin nodule showing blue clods (white arrow) over a gray background with peripheral brown pigment network (white arrow head, 20x, non-polarized, fotofinder GmBH). (D) Dermoscopy of skin nodule showing blue gray clods (white arrow) on a white back ground (20X, non-polarized, fotofinder, GmBH). (E) Dermoscopy of nodule over soles showing blue clods (black arrow) on a white background with brown dots (black arrowhead, 20x, non-polarized, fotofinder, GmBH).

Cutaneous neurocristic hamartoma is a rare hamartomatous proliferation of melanocytic, neuroid, and mesenchymal tissues. They show variable differentiation including melanocytic (nevoid, spindle cell, and dendritic), neurosustentacular (Schwann cell and perineural cells), and mesenchymal fibrogenic elements [2]. Congenital or acquired lesions present as pigmented macules, papules or nodules with or without alopecia. There is a predilection for the scalp. Benign NCH presenting as cutis verticis gyrata is very rare but has been reported [3].

Neurocristic hamartoma is a dermal dendritic melanocytic proliferation under borderline category [4] and shares histological features with blue and congenital nevi. Clinically, histopathologically, and even dermoscopically NCH can resemble a blue nevus. Dermoscopy of blue nevi showed a homogeneous, structureless pigment pattern, with either blue, white–blue, black, brown, and polychromatic [4]. The white-blue color was attributed to the oval/spindle cells the deeper location of the lesions within the dermis and the presence of a thicker subepidermal grenz zone and was seen more with hypochromic blue nevi [4]. Our patient had polychromatic lesions but predominantly blue gray and white clods. On histopathology had epithelioid/spindle cells with deep reticular dermis extension. The course of NCH is generally indolent, however, longstanding NCH has been reported to give rise to cutaneous malignant melanocytic neurocristic tumors [5].
Conclusions

Cutaneous NCH presenting as cutis verticis gyrata is rare. We have described the dermoscopic findings seen in our patient.

References


Figure 2. (A) Dermoscopy of scalp lesion showing blue gray clods (black arrow), white featureless areas, brown dots and streaks (black arrow head), multiple clustered dotted (white arrow) and linear vessels (20x, nonpolarized, fotofinder, GmBH). (B) Dendritic melanocyte (black arrow) with nests of nevus cells close to a nerve (H&E 40x). (C) Dermis showing spindle shaped cells with perineural distribution (white arrow) and cells seen involving the intervening stroma, with wavy nuclear contours (black arrow, H&E 40x). (D) Immunohistochemistry stain showing S 100 positive neural cells (S 100 40x). (E) Immunohistochemistry stain showing melanocytes stained with Melan A (black arrow, Melan A 40x).
Pilar Leiomyomas. Dermoscopy Pattern of a Rare Entity

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Case Presentation

A 60-year-old woman, with a personal history of a uterine fibroma, was seen for evaluation of multiple flesh-colored, erythematous papules and nodules localized on latero-cervical regions. Dermoscopic examination of all lesions revealed multiple shiny and whitish areas distributed homogeneously within a fine network in a single nodule (Figure 1A and B). The histological investigation confirmed a pilar leiomyoma.

Teaching point

The dermoscopic features of pilar leiomyoma tumor are not well defined, because of its rarity. It is similar to dermatofibroma with central hypopigmented area and peripheral network [1]. In our case the lesions presented widespread bright white areas, with a more regular shape respect to the “white like-cloud areas” reported by Diluvio et al [2].

Figure 1. A. Multiple flesh-colored, erythematous papules and nodules localized on latero-cervical regions. B. Multiples shiny whitish areas are distributed homogeneously over all lesions within a fine network.
References


Case Presentation

A 12-year-old boy presented with a 1-year history of slowly growing, 1.5 cm x 2 cm, livedoid, hard and depressed livedoid lesion on his back (Figure 1, A and B). Dermoscopic evaluation showed homogenous gray-whitish and livedoid large clods and crystalline structures (Figure 1C). The patient was referred for total excision. Histologically, fibro-histiocytic benign tumoral lesion located in a dense collagenized stroma separated from the epidermis by a cell-poor zone was observed. A few scattered lymphocytes were observed in between (Figure 1, D and E).

Teaching point

Atrophic dermatofibroma is a rare variant of dermatofibroma which was first described by Page and Assaad in 1987 [1]. It is commonly seen on the upper back of middle-aged women, and the mean age of the patients affected is 49.7 years, according to literature [1]. We present this uncommon entity, which is in the differential diagnosis with many benign and malignant lesions including atrophic scars, anetodermas, morphea, atrophic dermatofibrosarcoma protuberans and sclerosing basal cell carcinomas, as it is rare in the pediatric age group [2].
Figure 1. (A and B) Clinical presentation of a 1.5 cm x 2 cm, hard and depressed livedoid lesion on the back. (C) Gray-whitish and livedoid large clods with a homogenous distribution seen at dermoscopy. (D and E) Correlated histological images: fibro-histiocytic benign tumoral lesion located in a dense collagenized stroma separated from the epidermis by a cell-poor zone (H&E, x100, x200).

References


A Solitary Nodule Over the Chest

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Case Presentation

A 35-year-old male presented with an asymptomatic, subcutaneous mass with an overlying firm, red-brown nodule and shiny stretched skin (Figure 1A). On dermoscopy, an accentuated pigment network over background of pinkish color was seen. A few structureless focal white areas were present (Figure 1B). Histopathology revealed a poorly circumscribed dermal tumor with a clear grenz zone. The tumor consisted of monomorphic spindle cells with elongated hyperchromatic nuclei arranged in fascicles forming a storiform pattern (Figure 1C). Clinical, dermoscopic and histopathological features confirmed the diagnosis of dermatofibrosarcoma protuberans (DFSP).

Teaching Point

Dermatofibrosarcoma protuberans presents as an asymptomatic, slowly progressive indurated plaque that subsequently develops nodules. Dermoscopic features suggestive of DFSP are: delicate pigment network, vessels, structureless light brown areas, shiny white streaks, pink background coloration, and structureless hypo- or depigmented areas [1].

Mohs micrographic surgery remains the treatment of choice. Imatinib and sorafenib can be employed for unresectable and metastatic DFSP [2]. This report reinstitutes the importance of keen clinical and dermoscopic examination with histopathological correlation for timely diagnosis of this dermal tumor.
Figure 1. (A) Red-brown nodule with overlying shiny stretched skin present over right side of chest. (B) Dermatoscopy (DermLite™ DL3 - 3Gen under contact polarized mode) showing pinkish red background and unfocussed vessels (yellow arrow), accentuated pigment network (green arrowhead) and focal white areas (black arrow head). (C) Sections shows epidermis with grenz zone and underlying dermal tumor in storiform pattern. Entrapped adnexal structure and adipose tissue seen (H&E, 4x).

References


Retiform Hemagioendothelioma: Dermoscopic-pathological Correlation

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Case Presentation

A 31-year-old female presented with a single, asymptomatic, slowly growing, soft, cystic, dark-red nodule (with bluish periphery) of size 2 cm x 1 on the medial aspect of left upper thigh, of 4-5 years duration (Figure 1A). Dermoscopy revealed multiple deep red-colored globules of variable sizes separated by grayish white septae (Figure 1B).

Histology showed a tumor composed of infiltrating vascular channels, which was poorly circumscribed and was composed of partially compressed, anastomosing vessels lined by hobnail endothelial cells. The vessels were separated by attenuated fibrous walls. Immunohistochemistry was positive for CD34 highlighting the florid vascular proliferation.

Based on the above features, a diagnosis of retiform hemagioendothelioma was made.

Teaching point

Retiform hemagioendothelioma is a rarely infiltrative neoplasm, that mostly presents as an isolated growth, commonly involving the lower limbs [1,2]. Surgical excision has been used most commonly, although recurrences have been reported [2]. The unique feature observed was the grayish white septae separating the globules. Histologically, these septae conformed to the attenuated fibrous walls. To our knowledge, this is the first case describing the dermoscopic features for this entity.
Figure 1. (A) Clinical picture showing dark-red nodule. (B) Dermoscopy (Dermlite 10x) revealing multiple deep red-colored globules of variable sizes separated by grayish white septae.

References


Inflammatory Vitiligo

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Case Presentation

A 65-year-old man presented with multiple asymptomatic depigmented patches of varying sizes with an erythematous annular border over the upper back and shoulders for one week (Figure 1A). Histopathology from the border of one lesion revealed vacuolar interface changes and moderate perivascular lymphocytes with pigment incontinence in the superficial dermis. SOX10 staining revealed a reduction in epidermal melanocytes (Figure 1B). These findings were consistent with inflammatory vitiligo. After 2 weeks of 40 mg/day of oral prednisolone with a tapering dosage, the erythematous border had almost disappeared.

Teaching Point

The patterns of active and progressive vitiligo include inflammatory vitiligo, Koebner phenomenon, trichrome lesions, and confetti-like depigmentation. Inflammatory vitiligo is rare and characterized by erythema, scales, and pruritus at the border. Although the inflammatory phase is usually transient, it can cause rapid depigmentation [1]. Oral steroids are frequently used to stabilize rapidly progressive vitiligo, and ultraviolet phototherapy is another suitable treatment [2].
Figure 1. (A) Multiple asymptomatic depigmented patches with erythematous annular border over the upper back and bilateral shoulders. (B) Pathology with immunohistochemistry with SOX10 (100X): the right half of the figure from the erythematous border of the skin lesion shows the relatively normal distribution of epidermal melanocytes compared with reduced epidermal melanocytes in the left half of the figure from the depigmented area of the skin lesion.

References


A Particular Bicentric Structure in Dermoscopic Demonstration of Degos Disease

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Case Presentation

A 38-year-old woman suffered recurrent abdominal pain and rashes for 1 year. Physical examination showed multiple red papules with porcelain-white centers over her trunk and limbs (Figure 1A). Dermoscopic imaging demonstrated 2 yellow-white structureless centers of different sizes with telangiectasia, similar to a bicentric structure (Figure 1B). Histopathology showed intravascular thrombosis in the dermis (Figure 1C). Abdominal CT scanning confirmed small bowel perforation and abdominal adhesion. A diagnosis of Degos disease was made.

Figure 1. Clinical, dermoscopic, and histopathological figures (A) red papules with porcelain-white atrophic centers (B) two yellow-white structureless centers in different sizes with telangiectasia (C) epidermis atrophy, vacuolar degeneration of basal layer, increased collagen fibers, and intravascular thrombosis of the dermis.
Teaching point

Degos disease is characterized by unusual chronic thrombo-obliterative vasculopathy that affects small vessels. The histopathology of Degos disease is inconsistent, so dermoscopy may be helpful in making a definite diagnosis. The dermoscopic character of Degos disease is a homogeneous yellow-white structureless area in the center, surrounded by a circular hairpin-like small vessel [1,2]. Apart from the features mentioned previously, we noticed a particular bicentric structure, which is related to avascular necrosis caused by thrombosis.

References


Perinevoid Alopecia: an Unusual Presentation of Alopecia Areata

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Case Presentation

A 19-year-old healthy male complained of sudden onset of asymptomatic single patch alopecia on the occiput for three months. The round patch of non-scarring alopecia surrounded a pre-existent pigmented dome-shaped compound nevus, which did not change over time (Figure 1). Trichoscopic features were compatible with alopecia areata (AA), and the patient decided on conservative management.

Teaching point

Perinevoid alopecia (PA) is an extremely rare variant of AA associated with a central generally pigmented nevus [1]. Although the pathogenesis is still unclear, it is thought that PA is secondary to an inflammatory response against nevus cells or melanocytic structures [1,2]. Immune cells around the nevus attack the hair follicle, similarly to the destruction of melanocytes in a halo nevus, other nevocentric phenomena [2]. Surgical removal of the nevus may lead to hair regrowth a

Figure 1. A 1-cm diameter round patch of non-scarring alopecia surrounding a pre-existent pigmented dome-shaped compound subtype nevus on the right side of the occiput.
few weeks after excision [1,2]. Recognizing PA is essential to properly manage this unique variant of AA.

References


An Exuberant Case of Retentional Acne: Chloracne

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Case Presentation

A 39-year-old woman presented with an 11-year history of facial lesions. She had worked on tobacco, corn and bean plantings for 23 years, having contact with multiple pesticides. Physical examination showed open comedones and cysts, predominating on the malar region, over a grayish background (Figure 1, A and B). Her family history revealed 2 sisters with similar lesions, who had also worked in agriculture, while four other sisters without contact with pesticides, had no skin lesions. Laboratory exams were normal and skin biopsy showed diffuse hyperkeratosis and infundibular dilatation, with sebaceous gland disappearance (Figure 1C). At the moment, the patient is using isotretinoin 40 mg/day with a partial response, mostly on the open comedones. Furthermore, manual extraction of the larger retentional lesions was associated and she remains under follow-up.

Teaching Point

Chloracne is an acneiform eruption caused by the ingestion, inhalation or transcutaneous penetration of halogenated aromatic hydrocarbons [1]. These compounds induce hyperkeratinization of keratinocytes, transformation of sebocytes to a keratinocytic phenotype and increase melanogenesis [2]. Most importantly, the sudden onset of a large number of acneiform lesions in the same household should lead the physician to consider chloracne.
Figure 1. (A and B) Numerous open comedones and cysts over a light grayish background, predominating on the malar region. (C) Histopathology showing infundibular dilatation, diffuse hyperkeratosis and absence of sebaceous gland (H&E, x40).

References


Dermoscopy for Facial Leukotrichia in Vitiligo: an Important Step for a Better Treatment Decision

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Case Presentation

A 14-year-old female with stable generalized vitiligo (body surface area 1%) was being treated with excimer laser and tacrolimus 0.1% ointment. She showed some repigmentation in some body sites such as the knees. However, facial patches showed very minimal repigmentation despite receiving many sessions of excimer laser. Dermoscopy showed leukotrichia affecting the whole vitiliginous facial areas (Figure 1). The patient was therefore advised to undergo melanocyte transplantation. Topical and laser therapy were discontinued.

Teaching point

Leukotrichia within vitiligo is known to be associated with poor response to medical and light therapy. Therefore, it is important to identify leukotrichia in order to predict response to treatment within a given body site. It is often difficult to detect leukotrichia clinically especially in areas with fine vellus hair such as the face. Dermoscopy has recently emerged as a valuable tool in the assessment of vitiligo, especially for disease activity [1,2]. We find dermoscopy very helpful in detecting leukotrichia that cannot be seen clinically by the naked eye, especially for facial patches.
References


Iridescent Changes Observed During Dynamic Cross-polarized Dermoscopy

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Case Presentation

A 60-year-old male with skin phototype IV from Africa and a history of Kaposi sarcoma on his foot presented with a rapidly growing, 6.5-mm, bluish-purple nodule on his back. Cross-polarized dermoscopy using a DermLite DL4 (3Gen) coupled with an iPhone XS Max (Apple) revealed a ‘rainbow pattern’ on a structureless red background. By rotating the dermoscope without moving the smartphone during imaging, also known as dynamic cross-polarized dermoscopy, the color distribution within the rainbow pattern changed substantially (Figure 1, Supplementary Video 1). The lesion was excised and histopathologically confirmed as Kaposi sarcoma.

Teaching point

The metaphoric term ‘rainbow pattern’ is used to describe polychromatic structureless areas only seen with polarized dermoscopy. It has been described in several different skin tumors (eg Kaposi sarcoma, hemosiderotic dermatofibroma, angiokeratoma, aneurysmal atypical fibroxanthoma, melanoma and basal cell carcinoma) and other skin conditions (eg stasis dermatitis, lichen planus and scars) [1]. It is surmised that polarized light passing through slits created by parallelly aligned collagen bundles or vessels may cause the light to separate into different wavelengths [2]. Although the exact structures that actually cause the optical interference are unknown, the observed phenomenon is called iridescence. By applying dynamic cross-polarized dermoscopy, we demonstrate that the iridescence changes with the angle of polarization. This angular dependence of cross-polarized light has also been demonstrated previously by Marghoob et al on shiny white lines, which are only visible with the dermoscope positioned at specific angles.
References


Supplementary Video Legend

Supplementary Video 1. The iridescence or ‘rainbow pattern’ changes substantially while rotating the dermoscope relative to the smartphone camera (dynamic cross-polarized dermoscopy), thus demonstrating the angular dependence of polarization.
Dermoscopy as a Supportive Tool to Differentiate Lichen Amyloidosus From Clinical Mimickers

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Case Presentation

A 52-year-old woman presented with a 5-year history of itchy hyperkeratotic brownish papules on the legs (Figure 1A) dermoscopically typified by central brown globules surrounded by a pigmented halo (Figure 1B). Histology showed compact ortho-hyperkeratosis, irregular acanthosis, and amorphous eosinophilic material in the upper dermis which displayed positive Congo red staining and a green fluorescence under polarized microscopy (Figure 1C), consistently with a diagnosis of lichen amyloidosis.

Teaching point

Dermoscopy may be of aid in recognizing lichen amyloidosis by showing a peculiar pigimentary pattern resulting from the presence of melanin granules within amyloid deposition in dermal papilla (central globule) and basal layer hyperpigmentation/dermal pigment incontinence (peripheral pigmentation) [1]. Indeed, such dermoscopic clues are different from those visible in similar conditions, ie, pretibial pruritic papular dermatitis (dotted/globular vessels over a pinkish-white background) (Figure 1D), lichen myxedematous (white structureless areas) (Figure 1E), and lichen planus (Wickham striae) (Figures 1F) [1,2].
References


"Oak-leaf-like" Loop Vessels in Super-high Magnification Dermoscopy of Basal Cell Carcinoma

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Case Presentation

An 81-year-old patient presented with a 5-mm red firm ulcerated nodule on his back. Dermoscopy revealed ulceration in the center and linear irregular vessels distributed on the lesion’s periphery (Figure 1A). Optical super-high magnification dermoscopy (OSHMD) revealed looped vessels with extremely branched loops resembling oak leaves, which were distributed throughout the entire lesion (Figure 1B). The patient underwent excision of the lesion and diagnosis of nodular basal cell carcinoma (BCC) was established. A 49-year-old patient presented with a 4-mm plaque on the abdomen. Dermoscopy (Figure 1C) showed an image typical for BCC. OSHMD showed surprisingly numerous loop vessels in form of “oak leaves”, distributed across the entire lesion as well as in the previous case (Figure 1D). The established diagnosis was superficial BCC. The consent to publish data has been obtained from the patients.

Teaching point

In some cases, the diagnosis of BCC can be challenging. Therefore, the detailed dermoscopy, including analysis of morphology of the vessels is of the greatest importance. According to the literature, arborizing vessels are the most common type of vessels followed by the short fine tele-angiectasias, while the looped vessels are a minor vascular feature of BCC [1,2]. I have found looped vessels and named them “oak-leaf-like” because of their striking similarity to an oak leaf. As each of the images concerned a different subtype of BCC, it might be presumed that such complicated vessels do not depend on the thickness of the lesion.
References


Figure 1. Dermoscopy and super-high magnification dermoscopy images of basal cell carcinoma cases presented in the manuscript. (A) Ulceration in the center of the lesion and linear irregular vessels distributed on the red homogenous background on the periphery of the lesion (20x magnification). (B) Super high magnification dermoscopy (400x magnification) demonstrating looped vessels with extremely branched loops resembling “oak leaves”. (C) Arborizing vessels and short fine telangiectasias with a blue-gray globule (20x magnification). (D) Numerous loop vessels in the form of “oak leaves” (400x magnification). All images taken by the Foto Finder GmBH.
A Case of Melanoma in a Patient With Psoriasis Highlighting the Importance of Dermatoscopy and Inflammoscopy

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Case Presentation

A male patient in his fourth decade of life presented to the clinic for evaluation of psoriasis. Dermatoscopy of a lesion on the right posterior upper arm that clinically resembled a psoriasiform papule showed numerous polarizing-specific white lines and polymorphous vessels (Figures 1, A-C). Dermatoscopy of nearby papules and plaques of psoriasis revealed white scale on a background of randomly distributed dotted and coiled vessels (Figure 1D). The lesion in Figure 1A was sent for histological analysis and found to be a malignant melanoma with a Breslow depth of 0.7 mm, occurring in association with a nevus.

Teaching Point

Though clinically the melanoma resembled a psoriatic papule, under dermatoscopy the lesion appeared very different from other psoriatic lesions and had features of melanoma. This highlights the importance of dermatoscopy and inflammoscopy in the diagnosis of neoplasms and inflammatory conditions. The most common dermatoscopic pattern of psoriasis is erythematous background with evenly distributed red dots and white scale [1]. Polarizing specific white lines and polymorphous vessels, clues that can be seen in melanoma, would not be expected in psoriasis [2].
Figure 1. (A) Clinical image of the patient right upper arm with scattered pink papules and plaques with overlying white scale. (B) Close-up image of the patient right upper posterior arm showing an 8 mm erythematous papule with white scale. (C) Dermatoscopic view showing many polarizing-specific white lines and polymorphous vessels (polarized dermatoscopy). (D) Dermatoscopic view of nearby psoriasis showing white scale on a background of randomly distributed dotted and coiled vessels (polarized dermatoscopy).

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

References
