Dermoscopy in the diagnosis of cutaneous lymphoma (Review)

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Abstract. Cutaneous lymphomas are a group of rare and distinct diseases that present varying clinical manifestations, histopathology and prognosis. Optimal and early management relies on accurate diagnosis. Unfortunately, clinical diagnosis in early stages is difficult due to the clinical overlap with other dermatologic conditions. In numerous cases, several consultations and multiple biopsies are required. Dermoscopy is frequently used for the evaluation of melanocytic skin tumors, but its value has been recognized for non-melanocytic neoplasms and inflammatory skin diseases, and in the last few years it has assisted with the diagnosis of cutaneous lymphoproliferative disorders (LPD). Studies have shown that dermoscopy may be useful in the evaluation of cutaneous lymphomas, offering a link between clinical and histopathological examination, but the features are not diagnostic and histopathological confirmation is mandatory. However, dermoscopy can raise suspicion of cancer, leading to a skin biopsy. Furthermore, larger and prospective studies are required to define the exact dermoscopic features of every subtype of cutaneous lymphoma.

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Abbreviations: CTCLs, cutaneous T-cell lymphomas; CBCLs, cutaneous B-cell lymphomas; MF, mycosis fungoides; SS, Sezary syndrome; AD, atopic dermatitis; LPD, lymphoproliferative disorders; C-ALCL, primary cutaneous anaplastic large cell lymphoma; LyP, lymphomatoid papulosis; PCMZL, primary cutaneous marginal zone lymphoma; PCFCL, primary cutaneous follicle-center lymphoma; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type

Key words: dermoscopy, lymphoma, skin, diagnosis, lymphoproliferative disease

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1. Introduction

Primary cutaneous lymphomas are described as non-Hodgkin lymphomas involving the skin without extracutaneous manifestations when the diagnosis is established (1). Primary cutaneous lymphomas comprise a mixed group of cutaneous T-cell lymphomas (CTCLs) and cutaneous B-cell lymphomas (CBCLs) (1). CTLCs account for 75-80% of all primary cutaneous lymphomas and CBCLs for 20-25% (1). Optimal and early management of cutaneous lymphoma relies on accurate diagnosis. Unfortunately, clinical diagnosis, particularly in early stages is difficult to establish due to the clinical overlap with inflammatory conditions. In addition, histopathological diagnosis can be challenging as well due to absence of explicit diagnostic characteristics and a classification that frequently changes (2,3). In numerous cases, several consultations and multiple biopsies are performed to differentiate lymphoma from other inflammatory skin diseases. Recent data has demonstrated that mycosis fungoides (MF) is diagnosed with a delay of three years following the onset of the first symptom (4). As a consequence, dermatologists have searched for other diagnostic instruments to expedite the diagnosis (4).

Dermoscopy is a non-invasive procedure that provides a magnification of x10 of the cutaneous lesion, which allows the dermatologist to analyze the morphological structures that cannot be observed with the naked eye, structures that have a precise histological association (5). Dermoscopy is generally employed for the evaluation of melanocytic skin tumors, but it has been demonstrated to be useful for the assessment of non-melanocytic neoplasms and inflammatory skin diseases, and in the last few years it has aided with the diagnosis of cutaneous lymphoproliferative disorders (LPD) (4).

The purpose of the present review was to illustrate the dermoscopic characteristics of the most common forms of cutaneous lymphomas. PubMed, Medline and Scopus

databases were reviewed for articles published on dermatoscopic characteristics of cutaneous lymphoma. The key words 'lymphoma', 'mycosis fungoides', 'Sezary syndrome', 'dermoscopy', 'dermatoscopy' were used to identify studies assessing the dermoscopic features of cutaneous lymphoma. The reference list of included articles were manually searched for additional studies. Only articles published in English were considered.

2. Primary CTCLs

The most frequent CTCL is MF that represents ~60% of all cases, accompanied by primary cutaneous $CD30^+$ LPD and markedly rarer diseases such as Sezary syndrome (SS) (6).

MF. In early stages, MF is characterized by erythematous patches and plaques, lesions that may persist for a long period of time without influencing the survival of the sufferer (6). However, in ~30% of patients the disease progresses to advanced-stage disease, characterized by skin tumors and dissemination to lymph nodes, blood and internal organs, leading to a poor prognosis. Rarely, in the 'tumor d'emblee' variant, MF presents with tumors. In early stages, the differential diagnosis includes chronic dermatitis, psoriasis, parapsoriasis, contact dermatitis, and tinea corporis. In late stages, other types of lymphoreticular malignancies, metastases, sarcoidosis and cutaneous infections (deep fungal infections, leishmaniasis, leprosy, atypical mycobacterial infections) should be ruled out (7).

Besides the typical form of MF, other variants have been described: poikilodermatous MF, pagetoid reticulosis, granulomatous slack skin, folliculotropic MF, and hypopigmented/hyperpigmented MF (3).

Dermoscopy of early MF. The first study that assessed the dermoscopic features in patch-stage MF compared with chronic dermatitis was conducted by Lallas *et al* (8). The study included 32 patients with early MF (the stage of the disease was not specified) and 35 patients with chronic dermatitis. The authors reported that fine short linear vessels (sensitivity, 93.7% and specificity, 97.1%) and orange-yellowish patchy areas (sensitivity, 90.6% and specificity, 99.7%) are distinct criteria for the diagnosis. Furthermore, specific vascular structures resembling spermatozoa were observed in half of the cases, being less common but highly specific for the diagnosis. According to the authors, lesions of chronic dermatitis exhibit a dermoscopic pattern typified by dotted vessels. Besides the common appearance of fine short lines and orange-yellowish patchy areas, the authors described the appearance of purpuric dots, leading to a dermoscopic image comparable to that observed in pigmented purpuric dermatoses (8).

Xu *et al* conducted another study in order to determine the dermoscopic features of early MF, chronic dermatitis and plaque psoriasis (9). The study included 31 patients with early MF without specified stage, 36 patients with chronic dermatitis and 34 patients with plaque psoriasis. The authors reported that the most frequent dermoscopic characteristics of early MF were linear vessels with a regular distribution and a dull-red background with spermatozoa-like structures on the surface, along with orange-yellowish areas. A light-red background, white scales and regularly distributed dotted vessels were described in plaque psoriasis, while the frequently encountered dermoscopic features of chronic dermatitis were yellow scales and dotted vessels in a patchy distribution on a dull-red background. Due to the higher magnification used in the present study (x20), the authors observed a higher frequency of spermatozoa-like structures (sensitivity, 74.2% and specificity, 100%) (9).

Interestingly, in a study that evaluated angiogenesis in 25 patients, Bosseila *et al* revealed that MF exhibited a specific vascular pattern composed predominantly of dotted and linear blood vessels; orange-yellowish areas were noted in the background in a minority of cases (10).

In a study that investigated the dermoscopic characteristics of cutaneous lymphomas in order to search for any specific pattern, Ghahramani *et al* included 15 patients with a confirmed diagnosis of cutaneous lymphoma, as well as MF (11). In patch-stage MF, in all cases, dermoscopy revealed patchy white structureless areas with a fenestrated to trabeculated pattern, that resembled a 'celestial pattern of galaxies' (11). Fine short linear vessels and spermatozoa-like structures were observed in 71% of cases (11).

Ozturk *et al* realized the first prospective study, with long term follow-up in order to investigate the dermoscopic characteristics of stage IIA MF; the authors compared the findings with the ones found in plaque psoriasis (12). In stage II MF, orange-yellow patches (88.2%), short, fine and linear vessels (82.3%), geometric (rhomboid, triangular, parallel-shaped), fine, linear and white scales (70.5%), perifolicular white scales (47%) and white patches (35.2%) were frequent when compared with plaque psoriasis (12). Spermatozoa-like structures were observed in only 29.4% of cases, which was not statistically significant. The low proportion of spermatozoa-like structures was considered by the authors, a result of the lower magnification used in the study (x10) compared with previous studies (9,10). The lower magnification could not permit the differentiation between a spermatozoa-like structure and a dot/globule or linear vascular structure (12); this result was comparable with the one from the study conducted by Bosseila *et al* (10). Purpuric dots were identified in 35.2% of the cases (12), similar to the study of Lallas *et al* (8). The authors described for the first time in MF, the presence of linear white scales that form geometric shapes (rhomboid, triangular, parallel-shaped) and hypothesized that these structures may be the dermoscopic image of cigarette paper-like wrinkly scales. Additionally, in early-stage MF the authors described for the first time perifollicular and collarette white scales. The dermoscopic features of plaque psoriasis were dotted vessels, diffuse white scales and globular vessels (12).

Another prospective study was conducted by Wohlmuth-Weiser *et al* in order to evaluate CTCL patients using dermoscopy and high frequency ultrasound; the authors compared the findings with the ones identified in patients with atopic dermatitis (AD) and psoriasis (4). CTCL patches and CTLC plaques were analyzed separately. In CTCL patches the vascular patterns frequently observed were: fine short linear vessels, dotted vessels and spermatozoa-like structures. The authors revealed that spermatozoa-like structures exhibited a particularly specific dermoscopic feature for patch stage

CTCL in comparison with AD where this feature was not encountered. Dotted vessels, white and yellow scales were frequently encountered in AD (4). The dermoscopic characteristics of CTCL plaques included dotted vessels on a dull red background with white scales. Dotted vessels were common in psoriatic plaques, but spermatozoa-like structures were not encountered in any psoriatic patient. Interestingly, the study did not describe the orange-yellowish patchy areas found in previous studies (4,8,9).

Dermoscopy of foliculotropic MF (FMF). Histopathologically, FMF is different from the classic form of MF: There are folliculotropic infiltrates, and often the epidermis is spared. Clinically, FMF is localized frequently in the head and neck area, presents with follicular papules, acneiform lesions and alopecia (1). FMF has a more aggressive evolution than classic MF and usually does not respond to skin-directed therapy, although a recent study described a subgroup of FMF patients with a less aggressive behavior and an improved prognosis, such as in early stage MF (1).

Ghahramani *et al* were the first to describe the dermoscopic features of FMF, which appears to present with 'folliculocentric erosions surrounded by dotted (40%) and fine linear vessels (40%), loss of terminal follicles, and comedo-like openings' (11). Ozturk *et al* described scattered perifollicular white scales that were associated with perifollicular hyperkeratosis histopathologically (12). Perifollicular accentuation, and comedo openings were described in FMF patients in the study conducted by Wohlmuth-Weiser *et al* (4). Comedo-like openings may reflect follicular plugging and destruction of normal hair follicle architecture, while perifollicular accentuation may represent the atypical lymphoid infiltrate found within/adjacent to the hair follicle (13).

Interestingly, it was revealed that perifollicular accentuation in FMF, described as a white halo around the follicles, could be observed using higher magnification dermoscopy in lesions that do not clinically exhibit criteria for folliculotropism, as an early sign of folliculotropism (13). This accentuation of the follicle was not observed histopathologically in patients with MF without folliculotropism (13). Therefore, dermoscopy could be used for early recognition of FMF in patients who do not exhibit clinical signs of folliculotropism, allowing the selection of a suitable biopsy site (13).

Dermoscopy of poikilodermatous MF (PMF). Poikilodermatous MF, an uncommon form of patch-stage MF, presents as erythematous or brownish plaques covered by scales, atrophy, mottled pigmentation, and telangiectasia that are observed on the trunk and extremities (7).

Xu and Tan reported a case where they detected multiple polygonal structures composed of white storiform streaks, better observed in the center and less visible at the periphery. The holes intersecting the streaks were covered by hairpin vessels or fine red dots. Septa of pigmented dots unequally and sporadically distributed were described between the lobules. In addition, red and yellowish smudges were observed (14). Bosseila *et al* described a light brown focal hyperpigmentation as being characteristic for PMF (10).

Apalla *et al* described in a case report of PMF, dermoscopical linear branching vessels disposed as a network, on a pale pink to brown background, covered by fine scattered white scales (15).

Dermoscopy of pagetoid reticulosis. Pagetoid reticulosis is characterized clinically by a unique patch or plaque, psoriasiform or hyperkeratotic with a slow progression, typically located on the extremities (7). A case report has revealed using dermoscopy, that pagetoid reticulosis (Woringer-Kolopp type) exhibits a Bowen-like image: A homogeneous pink-erythematous background combined with dotted or glomerular vessels along with white scales (16).

Dermoscopy of granulomatous slack skin, a very rare form of MF, has yet to be reported in the literature.

Primary cutaneous CD30$^+$ T-cell LPD. Primary cutaneous CD30$^+$ T-cell LPD are the next most frequent group of CTCLs following MF, and they account for ~25% of all CTCLs. This group comprises primary cutaneous anaplastic large cell lymphoma (C-ALCL) and lymphomatoid papulosis (LyP). C-ALCL is described as solitary or grouped nodules and tumors, that rarely may be multifocal, with common cutaneous relapse, but rare extracutaneous manifestations. LyP presents as self-healing papulonecrotic or nodular skin lesions that have a chronic course and which are recurrent, with lesions in different stages of development being visible in the same patient (1).

Uzuncakmak *et al* described in a case report the dermoscopic aspect in C-ALCL: Pink to yellow structureless areas covered by polymorphous vessels that were more visible at the edge of nodular lesions (17).

In LyP dermoscopy is different according to the phase of the disease. The inflammatory stage is characterized by tortuous irregular vessels that are radially disposed, enclosed by a white structureless area. In the hyperkeratotic stage, the vessels are less noticeable and the whitish area prevails, while in the third stage, this whitish structureless area is replaced by a necrotic ulceration and the vessels are strictly visible on the rim of the lesion. The fibronecrotic area is visualized as a brown-greyish structureless area in dermoscopy. In the scarring stage, the brown-greyish structureless area persists, suggesting post-inflammatory pigmentation and there are no more residual vessel patterns (18,19). Ghahramani *et al* described dotted vessels and crystalline structures in LyP (11).

SS. SS is an uncommon leukemic form of CTC, defined typically by the triad of pruriginous erythroderma, generalized lymphadenopathy, and neoplastic T cells that have cerebriform nuclei (Sezary cells) and are found in the skin, lymph nodes, and peripheral blood (1). Differential diagnosis of early-stage SS and other erythrodermic inflammatory dermatoses is not easy to establish. Usually the patients are 55-60 years old, with a median overall survival of 63 months and a low 5-year survival rate of 28% (7). *Dermoscopy of SS.* Wohlmuth-Weiser *et al* used dermoscopy and high frequency ultrasound to define morphologic features of CTCLs and described two patients with SS, with individual patchy, well-defined skin lesions (4). The authors described a similar vascular pattern with the one observed in patch-stage MF, namely fine short linear vessels, dotted vessels and spermatozoa-like structures (4).

A recent study conducted by Rakowska *et al* assessed the role of trichoscopy in erythrodermic CTCL (erythrodermic MF or SS) (20). The hair follicles could be affected in erythrodermic CTCL due to folliculotropism of atypical lymphocytes that may alter the differentiation and maturation of the hair epithelium producing hair shaft abnormalities. The authors designed a study about the value of trichoscopy in aiding to differentiate erythrodermic CTCL from erythrodermic psoriasis and erythrodermic AD. A great many *pili torti* was the most sensitive and specific feature for erythrodermic CTCL (sensitivity, 81% and specificity, 93%), a feature that was not observed in other types of erythroderma, therefore numerous *pili torti* found in erythrodermic patients could represent a pathognomonic characteristic for erythrodermic MF or SS, imposing oncological diligence (20). Other dermatoscopic features identified were the following: Thick white interfollicular bands, eight-shaped hairs, color variation in the background (large reddish areas admixed with patchy brownish hyperpigmentation) and peculiar perifollicular disposal of glomerular linear vessels (20).

3. Primary CBCLS

CBCLs represent ~25% of all skin lymphomas and are divided in three main subgroups (WHO 2017): primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicle-center lymphoma (PCFCL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) (21).

Clinically, PCMZL presents as a solitary red to violaceous papule, plaque or nodule, located on the trunk or extremities in adult patients in their 50s; in PCFCL the lesions are typically found on the head of 60-year-old patients as pink to violaceous papules or nodules; and PCDLBCL-LT affects mainly elderly people (>75 years old) and is characterized by red to bluish infiltrated plaques, nodules or tumors found on the lower extremities (21).

Piccolo *et al* conducted the first study regarding dermoscopic examination associated with histopathology in 10 cases of primary CBCL characterized by a solitary red/pinkish nodule and revealed that the dermoscopic pattern was different from other diseases with the same clinical picture (3). As revealed using dermoscopy, most of the lesions included white circles found on a salmon-colored background/area, accompanied by scales and arborizing vessels. Arborizing vessels were smaller and more blurred compared with those observed in basal cell carcinoma (3). These findings were supported by case reports and small case series (3,22,23).

The largest study whose aim was to characterize the dermoscopic features of PCBCL, included 58 biopsy-confirmed lesions and was conducted by Geller *et al* (21). The authors observed that most of the lesions presented a salmon-colored background/area and pro-eminent serpentine vessels. No important differences in dermoscopic characteristics related to subtype of the disease or anatomic location were noted and other vascular patterns, scaling and ulceration were seldom described (21). The dermoscopic changes were not specific, and the authors concluded that dermoscopy should be integrated with the clinical findings (21).

4. Conclusions

Cutaneous lymphomas represent clonal proliferations of lymphocytes within the skin, that remain limited to the skin without evidence of extracutaneous disease at diagnosis. Early diagnosis represents a challenge due to the rarity of these diseases and to the clinical overlap with other skin disorders. Multiple studies have revealed that dermoscopy improves the diagnostic accuracy of skin tumors, in particular melanoma, basal cell carcinoma and squamous cell carcinoma (24-33), but only in the last few years, studies concerning the impact of dermoscopy in the diagnosis of cutaneous lymphoma have been conducted (7-21). They revealed that dermoscopy may be useful in the evaluation of cutaneous lymphomas, offering a link between clinical and histopathological examination, but the features are not diagnostic and histopathological confirmation is mandatory. However, dermoscopy may raise the suspicion of cancer, leading to a skin biopsy. Furthermore, larger and prospective studies are required to define the exact dermoscopic features of every subtype of cutaneous lymphoma.

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IC collected the literature. LU, AV, SCS and DB performed the literature review, manuscript drafting and critical revision of the manuscript for important intellectual content. Data authentication is not applicable. All authors contributed to manuscript revision, and read as well approved the submitted version.

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Competing interests

The authors declare that they have no competing interests.

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