Non-invasive techniques in the clinical diagnosis of cutaneous lymphomas

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Abstract

In clinical practice, cutaneous lymphomas can be challenging to diagnose or even suspect because they mimic a variety of other inflammatory and neoplastic dermatological conditions. Support for non-invasive skin analysis methods like reflectance confocal microscopy and dermoscopy is still anecdotic. Practically speaking, a deeper and more comprehensive study with a larger number of cases focusing on the effective usefulness of non-invasive techniques should be taken into consideration because they have demonstrated the ability to identify macro and micro features supporting the clinical suspicion of lymphomas, as well as being useful for differential diagnosis and supporting the selection of the biopsy site. The author provides a brief and narrative synopsis of the reflectance confocal microscopy and dermoscopy characteristics of cutaneous lymphomas in this manuscript.

Introduction

Diagnosis of cutaneous T lymphomas has to be done through the clinic-histologic correlation as both B- (CBCL) cell and T-cell lymphomas (CTCL) can resemble other dermatological conditions. During daily clinical activity, cutaneous lymphomas have to be suspected in general in cases of long-standing and poorly responsive skin lesions or fast development of single or multiple papules or nodules generally of red-violaceous color. In the case of CTCL, diagnosis is much less difficult in plaque and tumor stages than in early patch stage when mycosis fungoides (MF) simulate mainly psoriasis and eczema or many other inflammatory skin diseases.

Clinical assessment of skin tumours as melanoma or non-melanoma skin cancer with non-invasive techniques for skin analysis became progressively of routine. The application of these techniques on cutaneous lymphomas represents an interesting novelty that potentially can support the clinical suspect and drive the biopsy site selection for a faster and more conclusive diagnostic process. Here the author reports a narrative concise overview on dermoscopy and reflectance confocal microscopy (RCM) described features of cutaneous lymphomas.

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Dermoscopy in cutaneous lymphomas

Cutaneous T-cell lymphoma

Dermoscopy of MF has been described at first by Lallas *et al*. in 2012 describing dermoscopy features helpful in the differential diagnosis of early stages when specific features can be detected. In detail, two main features with high sensitivity and specificity can be seen in MF patch lesions as short linear vessels (93.7 of sensitivity and 97,1 of specificity), and orange-yellow patchy areas (sensitivity of 90,6 and specificity of 99,7). A peculiar, reported feature was the presence of spermatozoa-like structures described as having 99,7 specificity. On the counterpart, detection of yellow scales is more in favor of eczema (Figure 1).[1]

In the case of plaques and nodules, orange-yellow areas are the main dermoscopic features detectable in MF and other CTCL corresponding to dense dermal infiltration of neoplastic cells detectable on histology.

Later, in 2022, Errichetti *et al.* published a retrospective, observational, multicentric study on 118 MF cases considering different variants of MF (folliculotropic MF, erythrodermic MF and poikilodermatous MF) and describing dermoscopy features of plaques and tumors.[2] In detail, linear/linear-curved vessels and white scales in the skin furrows were significantly associated with patch-stage MF, while clustered dotted vessels were related to plaque-stage MF and peripheral linear vessels with branches, ulceration and red globules separated by white lines to tumor-stage MF. Moreover, patchy white scales were significantly more common in patches and plaques compared to tumors, whereas focal bright white structureless areas were related to plaque and tumoral stage. Vessels histopathologically corresponded to dilated vascular structures in the dermis, orange structureless areas to either dermal hemosiderin (patch/plaque stage) or dense cellular infiltration (tumors), bright white lines/structureless areas to der-

Table 1. Summary of the dermoscopy and confocal features characterizing B- and T-cell lymphomas.

Dermoscopy features of MF									
	Orange-yellow areas	Short linear vessels	Focal white and orange structureless areas	Spermatozoa-like structures	Clustered unfocused dotted vessels with branches	Peripheral unfocused linear vessels with branches	White scales in the skin furrows	Orange globules separated by white lines	Focal bright white structureless areas
MF patch	+	+		+			+		
MF plaque	+		+		+		+		+
MF tumors	+		+			+		+	+
Lymphomatoid papulosis	+		+			+		+	
CBCL	+		+			+		+	+
Distinctive dermoscopy features in MF variant									
Follicular MF	Lack of hairs	Dilated follicles	Follicular plugs						
Erithrodermic MF	Linear dotted vessels	Patchy white scales	Focal orange structureless areas						
Poikiloderma MF	Focal white and brown structureless areas	White patchy scales	Brown reticular lines						
Transformed MF	Large hyper-refractile roundish pleomorphic cells in the epidermis	Large hyper-refractile roundish pleomorphic cells in the upper dermis							
Confocal microscopy features									
	Single lymphocytes in epidermis	Disarranged epidermis	Aggregates of lymphocytes in the epidermis/Pautrier's abscesses	Lymphocyte at DEJ	Obscuration of DEJ	Dilated vessels	Thickening of the dermal fibres	Lymphocyte at upper dermis	Nucleated cellular infiltration and fibrosis in the papillary dermis surrounding the adnexa
MF patch	+	+	+/-	+	+/-	+/-			
MF plaque	+	+	+	+	+	+	+	+	
MF tumors				+	+	+	+	+	
Lymphomatoid papulosis	+	+	+	+	+	+	+	+	
CBCL						+	+	+	+
Distinctive confocal microscopy features in MF variant									
Follicular MF	Lymphocyte around and inside adnexal structures								
Transformed MF	Large hyperrefractile roundish pleomorphic cells inside the epidermis and in the upper dermis	Large hyperrefractile roundish pleomorphic cells in the upper dermis							

MF, mycosis fungoides; CBCL, Cutaneous B-cell lymphoma; DEJ, dermal-epidermal junction.

mal fibrosis and ulceration to loss of epidermis. The main dermoscopic findings of folliculotropic MF were lack of hairs, dilated follicles and follicular plugs, while erythrodermic MF was mainly characterized by linear/dotted vessels, patchy white scales and focal orange structureless areas and poikilodermatous

MF by focal white and brown structureless areas, white patchy scales and brown reticular lines.[2]

Errichetti *et al*., in 2022, published a second key multicentric study focusing on the dermoscopical features characterizing plaque and nodular lymphoma lesions and their differential diagnosis on a casuistic of 261 lesions of which 121 in the lymphoma group and 26 of T-cell lymphomas (17 CD30+ anaplastic large cell lymphomas and 9 CD4+ small/medium lymphoproliferative disorders).

In this paper, the main vascular findings of nodular/plaque-type lymphoproliferative condition in general (T and B) turned out to be the detection of unfocused linear vessels with branches (40% of the cases), unfocused dotted (29% of the cases) and linear-curved (28% of the cases) vessels, whereas focal white and orange structureless areas (54.5% of the cases) and white lines (42.1% of the cases; unspecifically arranged in 25.6%).

Presence of non-vascular dermoscopic feature as the presence of orange globules was significantly more common in the case of lymphoproferative conditions than in the control group of a miscellaneous non-lymphoproliferative neoplastic as well as inflammatory conditions underling the potential differential diagnosis with dermoscopy. In detail, a positive association between nodular/plaque-type lymphoproliferative skin diseases and the following findings: focal white and orange structureless areas, orange globules and white lines as been seen.

The dermatoscopic analyses according to histological subtypes revealed only 1 potent predictor for the differential diagnosis between B-cell and T-cell diseases as the presence of unfocused dotted vessels, which were significantly more common in T-cell proliferative conditions. No significant dermatoscopic difference was found among T-cell histologic subtypes.[3]

All the dermoscopy features characterizing T-cell proliferative diseases are summarized in Table 1.

Cutaneous B-cell lymphoma

In the case of CBCL in all the variants presenting clinically as firm nodules of the skin of red colour, dermoscopy is characterized by the presence of salmon-colored background, white circles/areas with arborizing vessels and or polymorphous vascular pattern (Figure 1).[4]

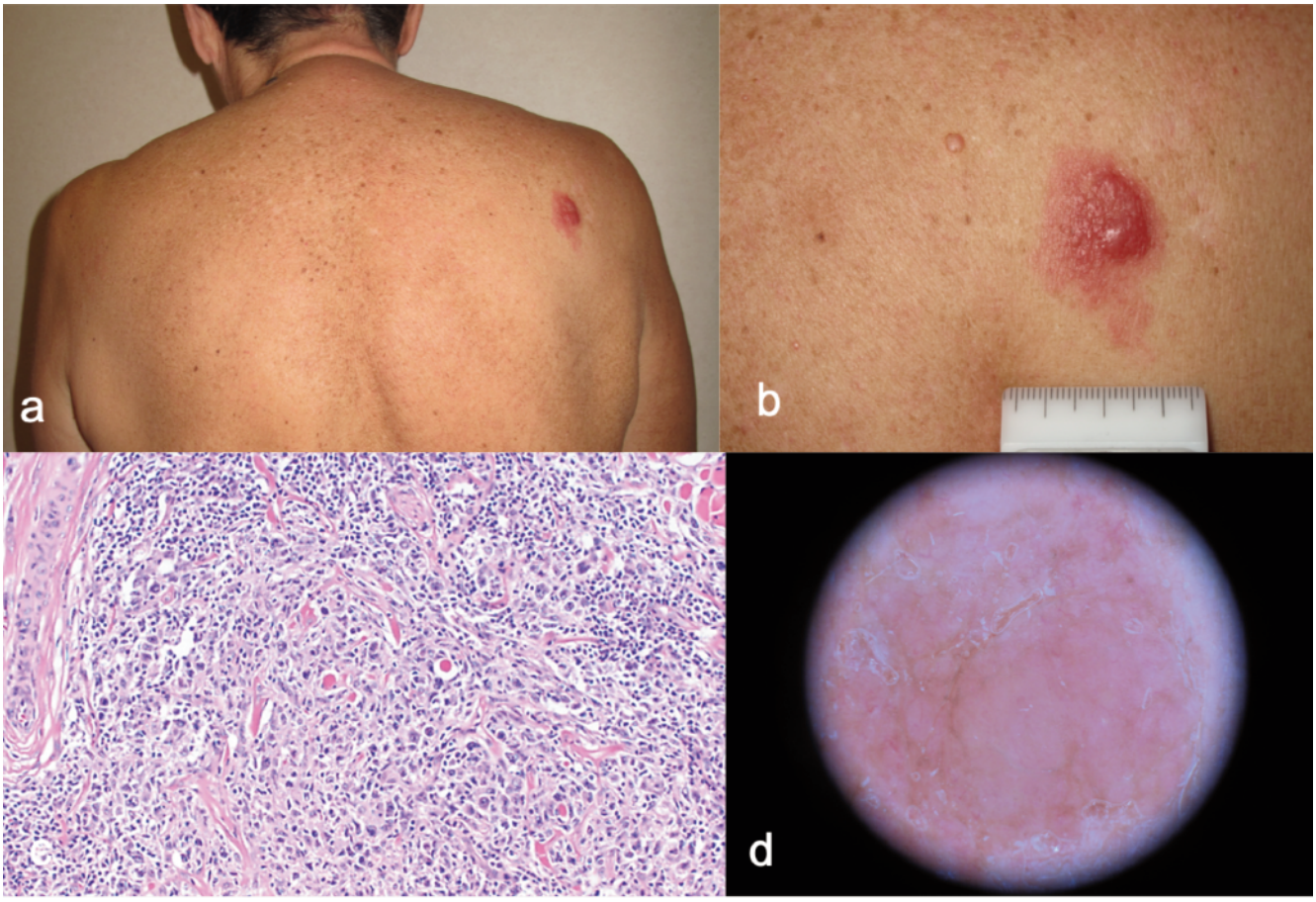

Figure 1. Clinical presentation of a firm nodule of the back of a 68-year-old man (a) and related detail of the erythematous, mammellonated nodular lesions (b). Dermoscopy showed the typical salmon-colored background, few white areas and polymorphous vascular pattern (d). Histopathology showed dense proliferation of atypical lymphocytes in the dermis diagnosed as marginal B-cell lymphoma (c).×).

Reflectance confocal microscopy in cutaneous lymphomas

Cutaneous T-cell lymphoma

RCM has been used in the diagnosis and treatment monitoring of CTCL. Its usefulness is limited to the depth of penetration of the papillary dermis and the limited refractivity of atypical lymphocytes. In addition, RCM does not allow performing immunohistochemical or molecular studies which can be crucial in the detection of CD30+ cells describing anaplastic large cell lymphomas of MF transformation. Nevertheless, RCM is a very valuable tool for differential diagnosis of other inflammatory diseases as interface dermatitis, psoriasiform dermatitis or spongiotic dermatitis. Moreover, RCM can be used for biopsy site selection in order to maximize the histopathological performance in order to reduce the time to diagnosis,[5-7] and support the treatment follow-up of CTCL.[8,9]

In the literature, several studies and mostly case reports have reported focusing mainly on MF and lymphomatoid papulosis (LyP). RCM showed the possibility of detection of epidermal involvement such as the presence of lymphocytes in the epidermis, and the dermal-epidermal junction (DEJ) and upper dermis infiltration of neoplastic cells with the limit of the impossibility of the analysis of the nuclear atypia.[10] Clinical-microscopical correlation at the bedside of the patient seems to represent a potential support to the suspect of CTCL.

The first RCM description of MF has been done. In 2007, by Agero *et al*.[4] on a series of 7 patients. They classified the features according to the clinical presentation: patch, plaque and tumor stages. They identified the presence of single lymphocytes (epidermotropism/exocytosis) in the epidermis seen as weakly refractile round cells, mostly in patch and plaque stages (Figure 2). Aggregates of lymphocytes in the epidermis have been reported mostly in the plaque stage and less in the patch stage, correlating histologically with Pautrier's microabscesses (Figure 2). Disruption of the normal dermal papillae and obscuration of the DEJ caused by atypical lymphocytes have been reported as signs of interface changes (Figure 2). Further studies confirmed the findings adding epidermal disarrangement,[8,11-13] dilated vessels,[12] and thickening of the dermal fiblres.[12] In the case of folliculotropic MF, lymphocyte infiltration has been detected around adnexal structures.[12,14] In transformed MF, large hyperrefractile roundish pleomorphic cells inside the epidermis and in the upper dermis have been reported.[13]

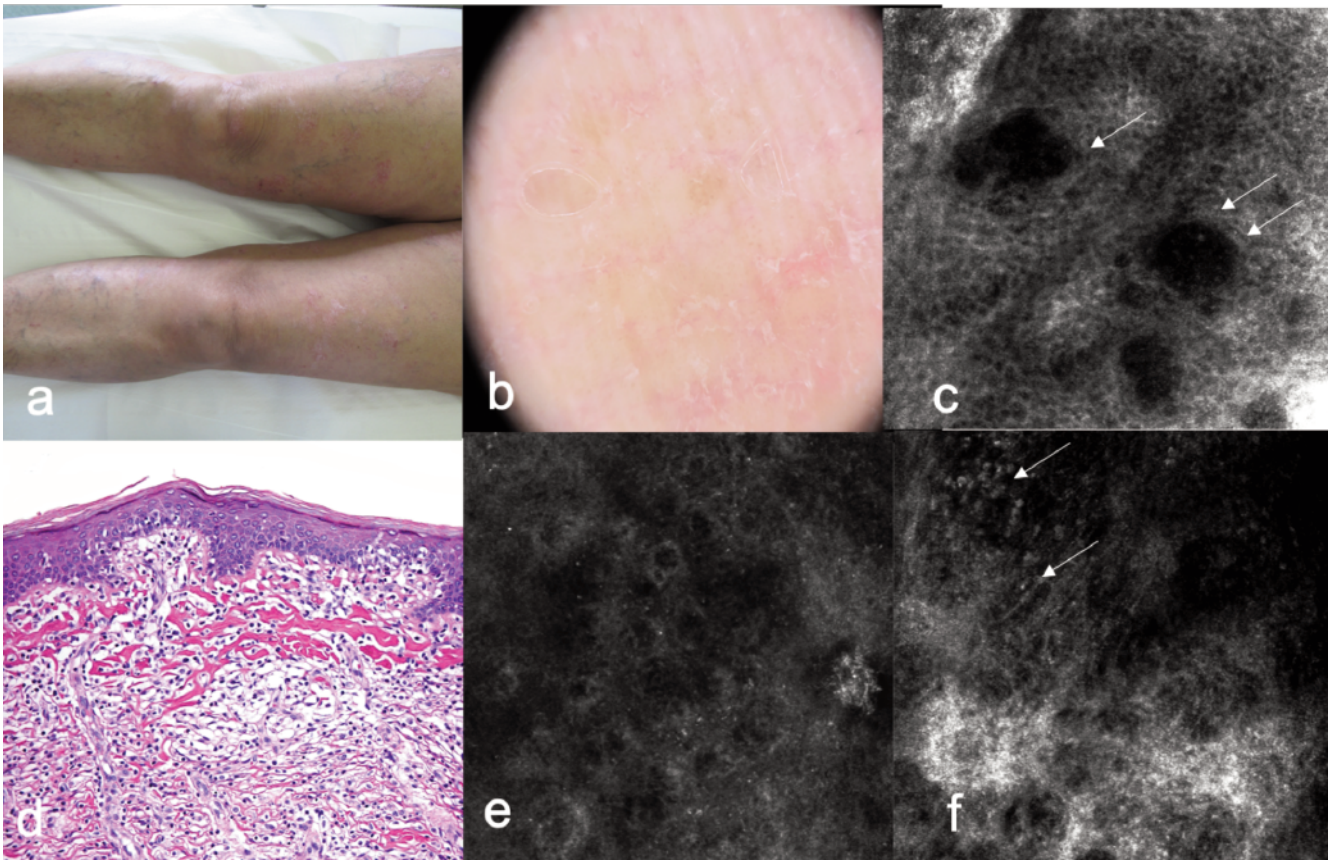

Figure 2. Clinical presentation of erythematous patches at the legs of a 68-year-old lady (a). Dermoscopy of one of the pathes showing short linear vessels and orange-yellow patchy areas. RCM showed dark areas corresponding to Pautrier's abscesses (arrows) (c), obscuration of the dermo-epidermal junction (e) and thick collagen bundles with dermal inflammatory cells (arrows) (f). Histopathology of mycosis fungoides with epidermotropism of lymphocytes and dermal sclerosis (d).

Koller *et al*. demonstrated that detection of interface dermatitis, exocytosis, dermal lymphocytes in the suspicion of MF have sensitivity and specificity respectively of 63.33% and 92.89% for differential diagnosis with interface, psorasiform, and spongiotic dermatitis.[15]

LyP has been firstly described in 2012 by Lange-Asschenfeldt *et al*.[13] in a series of CTCL patients.[13] In 2013, Ardigò *et al*. described the RCM features and their histopathologic correlates.[4] Similar findings to MF has been reported. Additionally, spongiosis, parakeratosis, dermal fibrosis and dermal lymphocytes in a significant number of cases have been described.[4]

All the RCM features characterizing T-cell proliferative diseases are summarized in Table 1.

Cutaneous B-cell lymphomas

Since CBCLs are by definition dermal proliferations, the description of RCM features in these tumors is anecdotal due to their limited depth penetration. Regarding skin CBCL, only one case has been reported by Laghi *et al.* who described a secondary cutaneous follicular B-cell lymphoma on the scalp with dermoscopy, RCM and histology.[17] In RCM, they identified nucleated cellular infiltration and fibrosis in the papillary dermis surrounding the adnexa, which corresponded to atypical lymphocytes on histology.

Conclusions

The use of non-invasive techniques supports the clinical suspect of cutaneous lymphomas adding initial microscopic information obtained at the patient's bedside and helpful at first for the differential diagnosis with other inflammatory and neoplastic skin diseases; second, both dermoscopy and RCM can be used for the biopsy site selection in order to avoid the needing of series of biopsies and excessive procrastination of the diagnosis. One of the most promising use of non-non invasive techniques is the treatment follow-up. Further studies, including a large number of cases and considering the different subtypes of cutaneous lymphomas, are needed in order to define the effective impact of those techniques on lymphoma patients.

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