A RETROSPECTIVE STUDY OF HISTOPATHOLOGIC CHANGES USEFUL IN DIFFERENTIATING EARLY PATCH/PLAQUE-STAGE MYCOSIS FUNGOIDES FROM MIMICKERS

STUDIU RETROSPECTIV ASUPRA MODIFICĂRILOR HISTOPATOLOGICE UTILE ÎN DIFERENȚIEREA DINTRE MYCOSIS FUNGOIDES- STADIUL INIȚIAL DE PLACĂ ȘI IMITATORI

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Abstract

Introduction: The diagnosis of Mycosis fungoides (MF) in its early stages is a complex process that requires integrated interpretation of clinical, histopathological, immunohistochemical and biomolecular data. Diagnostic uncertainty when assessing biopsies from suspicious lesions of early MF is a common problem encountered in dermatopathology.

Methods: In this study, a comparative analysis of microscopic changes present in 47 biopsies from early-stage lesions of 37 patients with confirmed MF and 30 biopsies from patients with various inflammatory dermatoses that mimic MF clinically or histopathologically was undertaken. Multiple histologic criteria were assesed, grouped into 5 categories: epidermal reaction, epidermotropism, presence of atypical lymphocytes, dermal reaction and dermal infiltrate.

Results: Statistically significant differences ($p<0.05$) were recorded for the presence of epidermotropic lymphocytes, atypical lymphocytes, dermal fibrosis and a "band-like" lichenoid infiltrate in the dermis. Spongiosis and presence of low numbers of eosinophils in the inflammatory infiltrate were not significant factors for exclusion of MF.

Discussion: In daily practice, when assessing biopsies taken from clinically suspicious lesions of early-stage MF, the absence of histopathological changes traditionally considered specific for MF should not prompt the exclusion of this diagnosis, an "wait-and-watch" attitude being more appropriate.

Keywords:

Mycosis fungoides, epidermotropism, Pautrier microabscesses, parapsoriasis.

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Rezumat

Introducere: Diagnosticul de micozis fungoides (MF) în fază incipientă este complex, fiind un proces care necesită o interpretare integrată a datelor obținute din investigații clinice, histopatologice, imunohistochimice și biomoleculare. Incertitudinea diagnosticului la evaluarea biopsiilor obținute din leziunile suspecte de MF incipient este o problemă frecvent întâlnită în dermatopatologie.
Metode: În acest studiu a fost realizată o analiză comparativă a modificărilor microscopice prezente în 47 de biopsii din leziuni de stadiu incipient prelevate de la 37 de pacienți cu MF confirmat și 30 biopsii de la pacienți cu diferite dermatoze inflamatorii care imită MF clinic sau histopatologic. Au fost evaluate mai multe criterii histopatologice, grupate în 5 categorii: reacția epidermică, epidermotropismul, prezența limfocitelor atipice, reacția dermică și infiltratul dermic.
Rezultate: S-au înregistrat diferențe semnificative statistic ($p < 0,05$) pentru prezența limfocitelor epidermotrope, a limfocitelor atipice, a fibrozei dermice și a infiltratului inflamator dermic "în bandă". Spongioza și prezența unui număr scăzut de eozinofile în infiltratul inflamator nu au reprezentat factori semnificativi de excludere a MF.
Discuție. În practica zilnică, atunci când se evaluează biopsiile prelevate din leziuni suspecte clinic de MF în stadiul incipient, absența unor modificări histopatologice considerate în mod tradițional specifice pentru MF nu ar trebui să determine excluderea acestui diagnostic, o atitudine de urmărire clinică atentă și eventual rebiopsiere fiind mai potrivită.

Cuvinte-cheie:

Mycosis fungoides, epidermotropism, microabcese Pautrier, parapsoriazis.

Introduction

Mycosis fungoides (MF), a neoplasm of skin-homing memory T cells, is the most often encountered type of cutaneous lymphoma[1]. Clinically, MF cases present with persistent skin lesions of varying size and shape, usually manifesting as patches that may gradually progress to plaques and eventually tumors. Patients in early patch and plaque stages typically show a favorable prognosis, however, some cases are prone to systemic spread with involvement of lymph nodes and internal organs[2].

Since the morphology of cutaneous MF lesions is variable, patients presenting especially early in the course of the disease can be mislabelled with different benign dermatoses, leading to delayed or inappropriate therapeutic measures. Many case reports and even a few systematic reviews have recognized early MF as one of the clinical masqueraders that can immitate a wide variety of inflammatory skin conditions, mainly with eczematous, psoriasiform and lichenoid characteristics[3],[4]. In such instances, there may also be challenges in differentiating early MF from its benign counterparts histologically, due to the fact that the reactive infiltrate usually overwhelm the malignant lymphoma cells. Uncertainty when assessing biopsies from clinically suspicious lesions of early MF is a major issue in dermatopathology, a definitive diagnosis requiring integrated interpretation of clinical, histopathological, immunohistochemical and biomolecular data, and sometimes clinicopathological follow-up[5]. In this study, we sought to further characterize the histopathologic features of MF in a Romanian population, by analyzing biopsies taken from patch/plaque stage lesions early in the course of their disease and comparing these features with those of various inflammatory dermatoses that mimic MF histopathologically.

Methods

A computer-driven quiery was performed at Colentina University Hospital, Bucharest, to retrieve all biopsies of centrally diagnosed MF cases received in the Department of Pathology between September 2009 and August 2014. We selected for the study only the cases that had a definitive diagnosis of MF in accordance with previously recommended criteria published by the International Society for Cutaneous Lymphoma (ISCL)(6). For every case there was available at least one biopsy from a patch/plaque-type lesion and selected cases were followed up for confirmation for at least one year, and up to six years from initial biopsy. We excluded the biopsies from tumoral lesions of MF, particular variants of MF, such as folliculotropic MF, granulomatous MF and the cases that showed unusual immunophenotype (CD8+ variant, CD30+ transformation). Due to the controversial nature of parapsoriasis, we also excluded all cases of small plaque parapsoriasis returned by the computer search. As per internal diagnostic protocols, cases of large plaque parapsoriasis are usually considered MF only when they meet minimum score for MF[6]. In every selected study case, the final diagnosis was established by correlating histopathologic

findings with clinical appearance and follow-up, using medical records, photographs taken during clinical examination, clinical evaluation or direct communication with the patient's physician. When two or three different biopsies were available from the same patient, all were included in the study.

The control group included various spongiotic, lichenoid or psoriasiform simulators of MF retrieved from files. Control cases were highly suspicious of early MF on histolpathogic grounds per original pathology reports, showing different features of MF, but in none of these cases MF was considered in the clinical differential diagnosis. All control cases were discussed in multidisciplinary team and they did not achieve ISCL criteria for MF[6] at the time of biopsy or during subsequent follow-up.

Hematoxilin and eosin (H&E)-stained sections were available for all biopsies belonging to study and control groups. Some cases had additional histochemical stains performed, such as periodic acid-Schiff and Perls. Immunohistochemical stains originally used for diagnostic purpose were not retrieved, since they were not subject of this study. All slides were randomized and blindly examined by two investigators under a multihead microscope (TT, RA). Multiple histologic criteria were assesed, grouped into 5 categories: epidermal reaction, epidermotropism, presence of atypical lymphocytes, dermal reaction and dermal infiltrate. Every feature was recorded as "-" (absent) or "+" (present, at least 25% of epidermal surface in one section). When a histologic feature was present only focally or in multiple isolated foci that summed up less than a quarter of a section, it was recorded as absent ("-"). A different semiquantification rule was used to assess the presence of certain cellular components in the composition of dermal infiltrate, namely eosinophils and plasma cells. They were considered present ("+") when minimum 5 cells could be counted in one tissue section. For statistical analysis, an online calculator was used to calculate a z-score for each criterion, which was subsequently converted to a two-tailed p value. Results were considered statistically significant for $p < 0.05$.

Results

Our initial search in the database returned 146 cases including "mycosis fungoides" term in the pathology report, during September 2009 and August 2014. Out of these, there was a total number of 47 biopsies from patch/plaque lesions obtained from 37 patients with MF that met the inclusion criteria for MF group. Slide specimens of all cases were available for analysis. From the same pool, a total of 30 biopsies of variuos histopathologic mimickers of MF met the inlcusion criteria in the control group, as described above. It contains the following entities that showed variuos histopathologic features of MF per original biopsy report: various eczematous dermatitides, including atopic dermatitis (13 cases, 43.3%), lymphomatoid contact dermatitis (1 case, 3.3%), lymphomatoid drug eruption (1 case, 3.3%), pigmented purpuric dermatitis (1 case, 3.3%), lichen sclerosus (3 cases, 10%), lichen simplex chronicus (3 cases, 10%), actinic reticuloid (1 case, 3.3%), pityriasis lichenoides chronica (3 cases, 10%), pityriasis

Table 1. Number and distribution of selected MF and control cases

	MF	Mimickers
Total cases	37	30
No. of biopsies available for study	N = 47	N = 30 Eczematous dermatitides, 13 Lymphomatoid contact dermatitis, 1 Lymphomatoid drug eruption, 1 Pigmented purpuric dermatitis, 1 Lichen sclerosus, 3 Lichen simplex chronicus, 3 Actinic reticuloid, 1 Pityriasis lichenoides chronica, 3 Pityriasis rubra pilaris, 1 Psoriasis vulgaris, 3
Average age, years	56.4	54.1
Range, years	25-81	24-82
Median age, years	60	57.5

rubra pilaris (1 case, 3.3%), and psoriasis vulgaris (3 cases, 10%) (Table 1). The average patient age for MF was 56.4 years (range 25-81 years; median 60 years). The average patient age for mimickers was 54.1 years (range 24-82 years, median 57.5 years). The MF cases were composed of 24 males (65%) and 13 females (35%), whereas the mimickers group was composed of 14 males (47%) and 16 females (53%) (Table 1).

There were several significant differences and overlapping features between MF cases and mimickers. The complete results of the randomized, blinded histologic assessment were detailed in Table 2 and particular features were illustrated in the photomicrographs. Major differences were recorded for the presence of psoriasiform hyperplasia of the epidermis, parakeratosis in elongated mounds, all types of epidermotropism, the presence of hypertrophic lymphocytes, papillary dermal fibrosis, papillary dermal edema, and disposition of dermal infiltrate. Morphologic features that could not be used to reliably differentiate MF from mimickers include the presence of spongiosis, some features of lymphocyte atypia, and low numbers of eosinophils in the dermal infiltrate.

Table 2. Comparison of histopathologic features between early MF and mimickers

	MF N = 47	Mimickers N = 30	z value (95% confidence level)	Two-tailed P
Epidermal reaction				
Spongiosis	17 (36.1%)	12 (40%)	-0.33	0.72
Psoriasiform hyperplasia	14 (29.7%)	20 (66.6%)	-3.17	0.001
Interface dermatitis	11 (23.4%)	6 (20%)	0.35	0.72
Epidermal atrophy	6 (12.7%)	2 (6.6%)	0.85	0.39
Parakeratosis	40 (85.1%)	19 (63.3%)	2.2	0.02
Epidermotropism				
Basilar lymphocytes	18 (38.3%)	5 (16.6%)	2.02	0.04
Pagetoid lymphocytes	21 (44.7%)	6 (20%)	2.21	0.02
Pautrier microabscesses	8 (17%)	0 (0%)	2.38	0.01
Disproportionate exocytosis	25 (53.2%)	5 (16.6%)	3.2	0.001
Lymphocyte atypia				
Cerebriform nuclei	2 (4.2%)	0 (0%)	1.14	0.25
Haloed lymphocytes	12 (25.5%)	7 (23.3%)	0.21	0.82
Hyperchromasia	3 (6.4%)	0 (0%)	1.41	0.15
Hypertrophic lymphocytes	12 (25.5%)	1 (3.3%)	2.53	0.01
Dermal atypical lymphocytes	1 (2.1%)	0 (0%)	0.8	0.42
Dermal reaction				
Papillary dermal fibrosis	39 (82.9%)	8 (26.6%)	4.94	<0.0001
Papillary dermal edema	5 (10.6%)	9 (30%)	-2.14	0.03
Purpura	8 (17%)	5 (16.6%)	0.04	0.96
Pigmented macrophages	6 (12.7%)	5 (16.6%)	-0.47	0.63
Dermal infiltrate				
Lichenoid band-like	34 (72.3%)	6 (20%)	4.48	<0.0001
Perivascular	20 (42.5%)	24 (80%)	-3.23	0.001
Eosinophils	6 (12.7%)	7 (23.3%)	-1.2	0.22
Plasma cells	2 (4.2%)	0 (0%)	1.14	0.25

Discussion

Mycosis fungoides is a potentially challenging diagnosis to make, especially in its early stages, when patients present to the dermatologist with erythematous patches and/or plaques of variable size and shape[7]. Even when the clinical appearance of the lesions strongly suggests MF, a biopsy may not bring histologic proof in favor of this diagnosis. The reasons may include, among others, the paucity and low frequency of anecdotic histopathologic criteria associated with MF, namely epidermotropism, Pautrier microabscesses and lymphocytes with cerebriform nuclei, the possibility that the biopsy site might be unrepresentative for the whole rash, or even the fact that MF infiltrates can masquerade as different reactive conditions that share similar patterns of inflamation, such as psoriasiform, lichenoid or eczematous diseases. Vice versa, even when classical clues of MF are present in a given specimen, their interpretation has to be carefully made, since various reactive inflammatory conditions have been reported to share similar histopathologic features with early MF, such as drug-induced T-cell pseudolymphoma[8],[9], lichen sclerosus et atrophicus[10], persistent pigmented purpuric dermatoses[11], actinic reticuloid[12], eczematous dermatitides[13],[14], lymphomatoid contact dermatitis[15], benign lichenoid keratosis[16], connective tissue disease[17], and skin infections and infestations[18],[19], among others.

In our study, we tried to comparatively assess the frequency of occurrence of different histopathologic criteria in biopsies from early lesions of MF, respectively from various entities that microscopically mimick MF. In the category of epidermal reaction (Figure 1) we investigated the appearance of spongiosis, psoriasiform hyperplasia, interface dermatitis, epidermal atrophy and the presence of elongated mounds of parakeratosis. A significant difference between MF and mimickers group was recorded for the presence of psoriasiform hyperplasia (29.7% in MF cases vs. 66.6% in control cases, p value = 0.001). In our opinion, this finding signifies a relative lack of epidermal reactivity as a response to the presence of lymphomatous infiltrate. When occured in MF cases, psoriasiform hyperplasia was rather irregular, lichen simplex chronicus-like, and was associated in a large proportion with a dense, band-like dermal infiltrate, finding which represents a combined psoriasiform and lichenoid pattern, as previousely described for MF[20]. Parakeratosis, manifested as a thin, long band on top of the affected epidermis, was observed more frequently with MF biopsies (85.1% vs. 63.3%, p value = 0.027), thus being relatively specific for early MF in certain situations. Focal spots of parakeratosis manifested as isolated columns and mounds of parakeratosis were more oftenly seen in the control group, but this feature was not recorded when parakeratosis band was not continuous over at least one quarter of biopsy section. A surprising feature was the presence of a low degree of spongiosis in relatively similar proportions in both groups (36% vs. 40%). In other words, spongiosis was a rather common event in early MF. This finding suggests that, when detected in biopsies for clinical suspicion of early MF, a low degree of spongiosis should not be the sole criterion for MF exclusion.

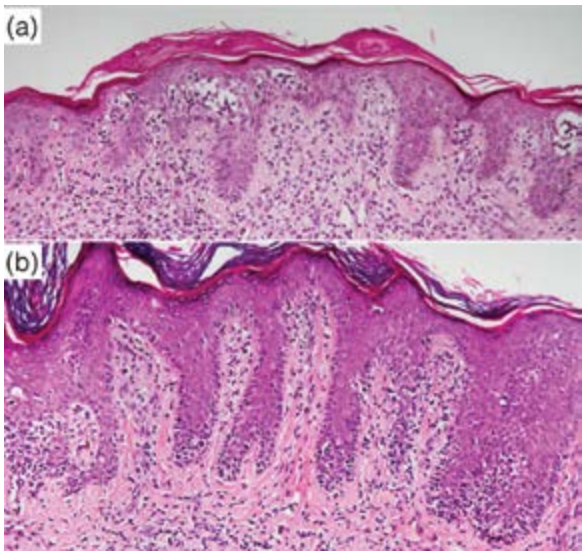

Figure 1. Epidermal reaction in patch/plaque-stage MF: (a) Spongiosis; (b) Psoriasiform hyperplasia.

To be able to quantify the degree of epidermotropism, we looked for various patterns described before in patch and plaque-type MF[21],[22], like the presence of lymphocytes aligned along the basal layer of the epidermis (basilar lymphocytes), a diffuse spread of lymphocytes into the epidermis (pagetoid lymphocytes), the presence of lymphocytes in clusters larger than 3 cells (Pautrier microabscesses) and areas of spongiosis where exocytosis of lymphocytes overwhelms the degree of intercellular edema usually seen with spongiotic dermatitides (dysproportionate exocytosis) (Figure 2). At least one type of epidermotropism was detected in 44/47 MF biopsies (93.6%) vs. 14/30 (46.6%) control biopsies (P < 0001). A noteworhty feature was the occurrence of dysproportionate exocytosis in MF cases as compared to mimickers (53.2% vs. 16%, p = 0.001). This finding correlates with the frequency of spongiosis detected in MF cases. In the same time it confirms that spongiosis may not be a truly exceptional event in early MF, but when joined by a dysproportionate number of lymphocytes in the epidermis, it may even be a feature of MF. Another notable observation regards the presence of Pautrier microasbscesses, defined as collections of intraepidermal lymphocytes devoid of spongiosis. Their presence correlates well with MF, since this feature was recorded in none of the control cases. However, in some cases belonging to the control group and labeled as spongiotic dermatitis, there could be spotted intraepidermal collections of nonlymphoid cells with abundant eosinophilic cytoplasm and a larger, pale, some-

times indented nucleus with a conspicuous nucleolus. They represent clusters of Langerhans cells that have been described before as pseudo-Pautrier abscesses, and usually appear in association with inflammatory dermatoses[23]. Their occurrence should not be regarded as a histopathologic clue for MF. Besides their cytologic features, the pseudo-Pautrier collections commonly develop in a background of spongiosis, a feature that may help in their discrimination from real Pautrier microabscesses, which are devoid of spongiosis.

Although traditionally linked to cutaneous lymphoma, lymphocyte atypia has been found by different investigators to represent a subjective criterion, which sometimes is difficult to assess[24],[25],[26]. Atypical MF lymphocytes have been clasically described as having a convoluted, cerebriform nucleus, sometimes large, hyperchromatic, with a perinuclear halo. We tried to independently asses all these features in our study, and observed that less than one quarter of MF cases showed at least one form of lymphoid atypia (Figure 3). Although rarely seen in early stages, the specificity of this finding is very high for MF, equal to or nearly 100%, since the presence of atypical lymphocytes in the epidermis of reactive dermatoses was a extremely rare event. The single most frequent atypical feature in the control group was the perinuclear halo, which can be possibly interpreted as a processing artefact. Together with hyperchromasia, it had no discriminatory value between MF and mimicker groups. Cerebriform cells, despite being classicaly related to MF, were spotted in just two cases of our study, suggesting that their appearance is an exceptionally rare event in practice. One reason for that may be of technical nature, since cell morphology can be influenced by section thickness, tissue processing protocol, staining etc. The occurrence of hypertrophic lymphocytes was the most reliable feature of atypia, reaching statistical significance (25.5% vs. 3.3%, p = 0.011).

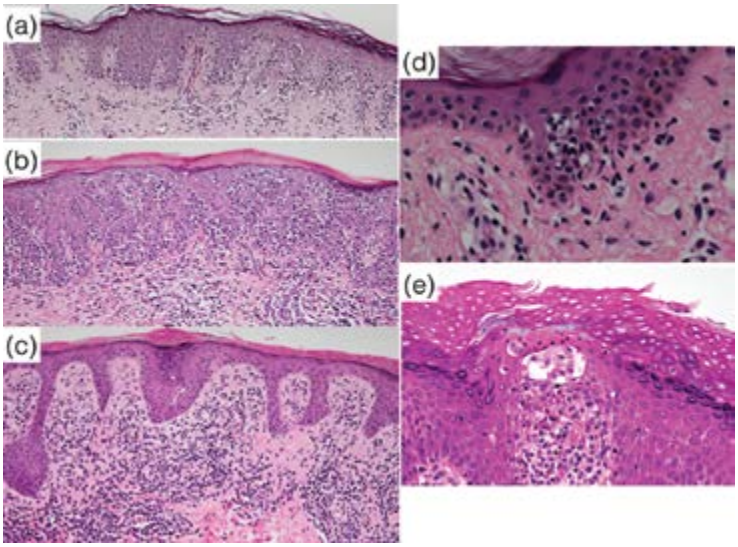

Figure 2. Patterns of epidermotropism: (a) Basilar lymphocytes in MF; (b) Pagetoid lymphocytes in MF; (c) Pautrier microabscess in MF; (d) Pseudo-Pautrier abscess in eczematous dermatitis; (e) MF without epidermotropism.

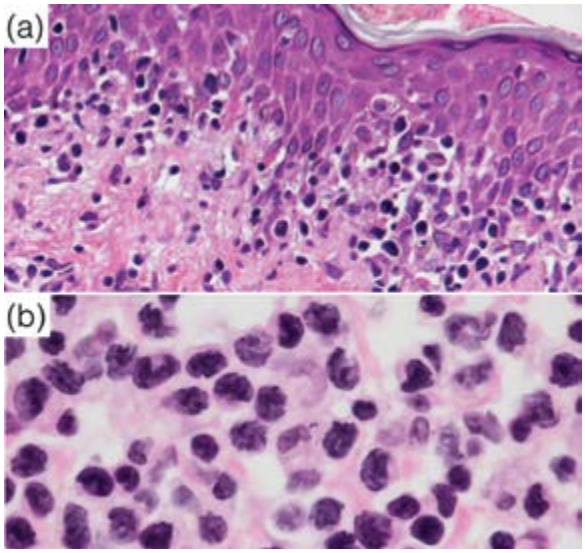

Figure 3. Lymphocyte atypia in MF: (a) Hypertrophic and hyperchromatic tumoral lymphocytes at the dermal-epidermal junction; (b) Cerebriform lymphocytes in dermal infiltrate.

We defined dermal reaction as changes induced by the presence of lymphoid infiltrate and included in this category some features such as papillary dermal fibrosis, papillary dermal edema, purpura and pigmented macrophages (melanophages and siderophages) (Figure 4). Similar to other studies[27],

a statistically significant difference was noticed for papillary dermal fibrosis, feature commonly seen in MF group (83% vs. 26.6%, $p < 0.0001$). The presence of coarse, haphazardly oriented "wiry" collagen bundles in the upper dermis is one of the most reliable signs of patch and plaque-type MF, probably signifying the longstanding presence of the infiltrate at dermal level[20]. It might be determined by the interaction of tumoral cells and their cytokine secretion with matrix proteins and matrix remodelation[28]. Edema of the papillary dermis was deemed unusual in MF by other investigators, although it was recorded in some of our MF cases. For example, in the largest series of MF cases to date, Massone et al. recorded no papillary dermal edema in 745 biopsies[22]. The presence of papillary dermal edema in 10.5% of our MF cases migh correlate with the presence of spongiosis in MF. All other dermal reaction changes did not reach statistical significance between the groups. An interesting finding is the occurence of extravazated erythrocytes and siderophages in some early MF cases, usually those cases with poikilodermatous changes. Purpura was seen with similar frequency in both our groups. When attempting a histopathologic diagnosis, the presence of siderophages naturally brings into question the possibility of a pigmented purpuric dermatosis (PPD). In some patients, MF and PPD have been shown to coexist[29], a finding challenged by other investigators[11],[30].

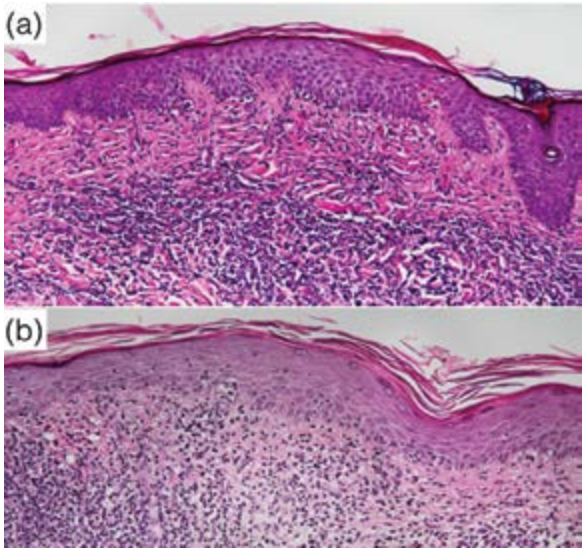

Figure 4. Dermal reaction in MF: (a) Fibrosis of papillary dermis; (b) MF with purpura and siderophages (PPD-like).

Regarding the distribution of the dermal infiltrate (Figure 5), the lichenoid pattern defined as a dense, band-like infiltrate in the upper dermis correlated well with MF lesions (72.3% vs. 20%, $p < 0.001$). The presence of a dense lichenoid infiltrate usually explains the palpable nature of the plaque-type MF lesions, and when seen in biopsies along with other architecutral changes, like psoriasiform epidermal hyperplasia, can be highly indicative of MF in appropriate clinical setting. But similar patterns of inflamation can be manifested in cutaneous biopsies of secondary syphilis, actinic reticuloid, lichen simplex chronicus among others, thus the architectural criteria alone are insufficient for the diagnosis of MF[31]. On the other hand, a strictly perivascular infiltrate is rather common in reactive dermatoses and make MF unlikely, unless epidermotropic features or atypical lymphocytes are obvious. When looking at the composition of dermal infiltrate, there were 6 biopsies in MF group (12.7%) in which low numbers of eosinophils could be detected, at a density of minimum 5 eosinophils per section in at least one tissue section. Similarly, eosinophils were recorded in 23.3% of control cases ($p = 0.22$). There was no statistical difference between gropus, meaning that the presence of low numbers of eosinophils in the dermal infiltrate could not be used as a histopathologic criterion to certainly rule out early MF. None of the mimicker cases showed higher number of eosinophils. A reason for the relative paucity of eosinophils in the mimickers group might be the fact that cases with overtly more eosinophils in the infiltrate were not selected, because they did not fulfill the criteria of histopathological mimickers of MF. Contrary to our finding, Dalton et al. showed that the presence of eosinophils is unusual for early MF lesions, being a marker for spongiotic dermatitis[32]. However, their threshold was set at a minimum of 3 eosinophils per section, and under this value, the autors stated that MF couldn't be excluded when evaluating a biopsy that lacks other convincing criteria of exclusion. An argument for the presence of eosinophils in some of our early MF lesions might be unknown previous treatment of lesions with topical agents,

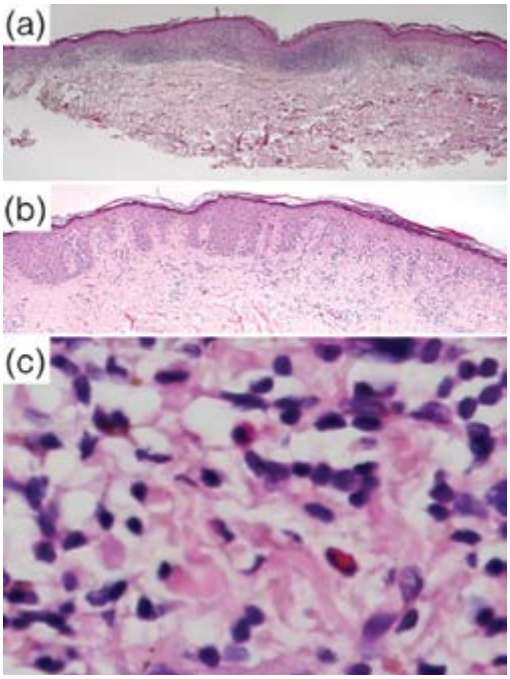

Figure 5. Features of dermal infiltrate: (a) Lichenoid infiltrate in MF; (b) MF with sparse perivascular infiltrate; (c) Eosinophils in MF.

especially in the setting of a clinically unresponsive rash.

Conclusions

In our series of Romanian patients with early stage MF, we confirmed that the presence of epidermotropic lymphocytes, atypical lymphocytes, upper dermal fibrosis and a "band-like" lichenoid infiltrate are reliable histopathologic features. All subtypes of epidermotropism gained high specificity for early MF, but their sensitivity was usually low to be used as pivotal diagnostic criteria. Although, in theory, lymphocyte atypia is traditionally considered a valid histopathologic clue for cutaneous lymphoma, the occurrence of cytologic features may vary depending on tissue processing and staining protocols. Additionally, our study showed that morphologic criteria routinely assigned to reactive conditions, such as spongiosis, eosinophils and purpura with siderophages, were present in similar degrees in both case groups and may not allow differentiation of MF from mimickers.

Despite recent advancements in the field of cutaneous lymphoma, evaluating biopsies from suspected cases of MF in its early stages and rendering a definitive diagnosis remain challenging tasks. Provided the biopsy is accompanied by comprehensive clinical history, good description of the lesions, clinical pictures and efficient communication with reffering physician, we believe that a diagnosis of MF can be made with confidence. In certain cases, however, relying just on histopathologic criteria might prove erroneous, since there is no single criterion sensitive and specific enough to discriminate between early MF and a pletora of reactive inflammatory rashes. In daily practice, when assessing biopsies taken from clinically suspicious lesions of mycosis fungoides, the pathologist should not promptly exclude this diagnosis based solely on absence of traditional histopathologic changes, integrative interpretation together with clinical and ancillary data and possibly an "wait-and-watch" attitude being more appropriate.

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