



Original Research

Defining the mimics and clinico-histological diagnosis criteria for mycosis fungoides to minimize misdiagnosis^{☆,☆☆}



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ABSTRACT

Background: Mycosis fungoides (MF) is a significant diagnostic challenge; it has various differential diagnosis especially at an early stage. Our aim was to describe mimics of MF clinically and histologically, and to define significant diagnostic criteria of the disease.

Methods: This was a retro-prospective cohort of 370 patients in whom the diagnosis of MF was suspected clinically.

Results: MF was histologically confirmed in 15.4% of cases and rejected in 84.5%. Other identified histologically diagnosis were eczema, psoriasis; nonspecific dermatitis, lichen, lupus; pseudolymphoma, parapsoriasis and toxidermia. 4 patients with palmoplantar MF were wrongly treated as eczema, and 10 patients with psoriasisiform MF were initially treated as psoriasis. We also described the clinical, histological and immunohistochemistry diagnostic criteria for distinguishing MF from benign dermatosis.

Conclusions: Misdiagnosis of MF was a real problem for this study, because it shared common clinical and histological characteristics with other inflammatory diseases like eczema and psoriasis. Therefore, defining significant clinico-histological diagnosis criteria of MF would be of great help and would increase the accuracy of the diagnosis.

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Introduction

Mycosis fungoides (MF) is the most common primary form of cutaneous lymphoma (Ahn et al., 2014) and accounts for almost 50% of all these types of lymphoma (Doukaki et al., 2009; Whittaker and Foss, 2007). MF affects most commonly middle-aged and elderly adults of all races Hwang et al., 2008; Scarisbrick, 2006) who usually present with persistent and/or slowly progressive skin lesions of varying sizes and shapes (Fatemi Naeini et al., 2015; Jang et al., 2012). The natural history of MF is characterized by an indolent progression through four disease stages: patch, plaque, tumor, and visceral involvement (Kazakov et al., 2004; Kim-James and Heffernan, 2001; Zinzani et al., 2008) Less than one-third of patients with MF develop advanced disease that involves lymph nodes, blood, and visceral organs (Howard and Smoller, 2000; Hwang et al., 2008; Kim et al., 2003; Massone et al., 2005; Paulli and Berti, 2004; Pope et al., 2010; Song et al., 2013).

Although MF was first described in 1833 (Ahn et al., 2014) and our understanding of this disease continues to evolve, MF remains a significant diagnostic challenge (Arps et al., 2014; Diwan, 2016; Nashan et al., 2007; Ngan et al., 2014; Oschlies and Klapper, 2013) because it can have different diagnoses on the basis of clinical and histological test results, especially at the early stage of the infection (i.e., mainly inflammatory dermatoses). Despite advances in immunohistochemistry and molecular diagnostics, false-positive, false-negative, and indeterminate diagnoses are not uncommon. In most cases, the overall balance of clinical versus immunophenotypic features must be considered carefully, which may favor or exclude inflammatory and reactive processes.

The objective of our study is to define the entities that mimic the diagnosis of MF on the basis of clinical and histological test results and define the criteria to diagnose MF in the Moroccan population.

Materials and methods

This was a unicentric, observational, and descriptive retro- and prospective analysis of hospital data (retrospective from 2008 until June 2013 and prospective from June 2013 to March 2014) from

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patients who were diagnosed with MF on the basis of clinical test results. Patient data were collected by doctors of the Department of Dermatology at the University Hospital Hassan II of Fez in Morocco. Informed consent was obtained from all patients.

The medical records of patients included sociodemographic data (i.e., age, gender, employment status, ethnicity, disease duration, personal or familial atopy, personal or family history of psoriasis, exposure to toxicity or irradiation), clinical data such as functional symptoms (i.e., deterioration of general condition, pruritus, pain) and physical signs (i.e., patches, plaques, nodules, tumors, erythroderma, scalp, nail and mucosal involvement), and laboratory test result data (i.e., standard histology and immunohistochemistry test results).

For the standard histology technique, cutaneous tissues that were taken from biopsy specimen were required to be preserved (fixed) and cut into sections that were thin enough to be translucent. After fixation, the tissue sections were dehydrated in alcohol, infiltrated with paraffin, and cut on a microtome. To preserve the section that was made from a block of fixed tissues, it is mounted on a glass slide and covered with a thin cover glass with a transparent substance that hardens and seals the preparation to make it permanent. The staining process is based primarily on hematoxylin and eosin stains, after which the tissue section is examined under a microscope.

The immunohistochemistry was based mainly on cluster of differentiation (CD) 3, CD4, and CD30 as markers of T-cell lymphoma and MF, and on CD20 to exclude B-cell lymphoma.

Descriptive and univariate analyses were conducted with the SPSS Statistics 20 software. In the descriptive analysis, quantitative variables were expressed as means \pm standard deviation and qualitative variables as percentages. In the univariate analysis, the comparison of two percentages was carried out by the χ^2 test. *p* values less than .05 were considered statistically significant and the power factor was 80%.

Results

The series included 370 cases and included 196 male (52.7%) and 174 female patients (47%). The average patient age was 50.5 years (SD = 17 years) and 255 patients (68.9%) were aged more than 45 years. A total of 161 patients (43.5%) had a disease duration between 5 and 10 years. Ten patients (2.7%) with psoriasiform MF were first treated for psoriasis before the diagnosis was confirmed with histology test results and four patients (1.08%) with palmoplantar MF were treated initially for eczema.

Pruritus was present in 67.8% of cases and the main clinical signs in patients were erythematous scaly patches (38.10%), pigmented patches (22.20%), nodules (13%), tumors (11.40%), erythroderma (12.2%), lymphadenopathies (14.30%), palmoplantar keratoderma (8.40%), poikiloderma (2.4%), scalp involvement as follicular papules and alopecia (13.50%). Of these lesions, 43.2% were localized to the covered areas.

On the basis of histological test results, a diagnosis of MF was confirmed in 57 cases (15.4%) and rejected in 313 cases (84.5%; Table 1). Fifty-two patients with MF (91.2%) had classical MF (Figs. 1–4), and five patients (8.7%) had variants of MF including folliculotropic MF in 3 cases, transformed granulomatous MF CD30+ in one case, and transformed MF CD30- in one case (Table 2). Other differential diagnoses that were identified on the basis of histological test results were primarily eczema (Fig. 6), psoriasis (Fig. 7), nonspecific dermatitis, lichen (Fig. 8), lupus, pseudolymphoma, parapsoriasis, and toxidermia.

The main signs that were found in the histological test result data of the patients with MF included epidermotropism in 51 patients (89.4%), Pautrier microabscess in 17 patients (29.8%), superficial lymphoid infiltrate in 40 patients (70.1%), bandlike appearance in 15 patients (26.3%), clear cytoplasm (haloed cells) in 27 patients (47.4%), and enlarged hyperchromatic cerebriform nuclei in 10

Table 1
Epidemiological, clinical, and histological characteristics of the study population

Study Population Characteristics	Number (of 370 patients)	Percentage	
Age groups	≤15 years	2	0.6%
	15–45 years	113	32.4%
	45 years	255	68.9%
Gender	Female	174	47%
	Male	196	52.7%
Disease duration	≤5 years	136	42.1%
	5–10 years	161	43.5%
	≥10 years	73	22.6%
History of psoriasis in patients who were later confirmed histologically with MF	10	2.7%	
History of eczema in patients who were confirmed histologically with MF	4	1.08%	
Pain	14	3.8%	
Pruritus	251	67.8%	
Deterioration of general condition	13	3.51%	
Erythematous plaques	78	21.1%	
Erythematous scaly patches	141	38.1%	
Papules	44	11.9%	
Nodules	48	13%	
Pigmented patches	82	22.2%	
Ulceration	6	1.6%	
Tumors	42	11.4%	
Erythroderma	45	12.2%	
Depilation of the body	11	3%	
Poikiloderma	9	2.4%	
Ichthyosiform state	3	0.8%	
Palmoplantar keratoderma	31	8.4%	
Lymphadenopathies	53	14.3%	
Scalp involvement	50	13.5%	
Nails involvement	29	7.8%	
Leonine facies	5	1.4%	
Localization in covered areas	160	43.2%	
MF rejected histologically and retained diagnosis of	Eczema	59	14.3%
	Psoriasis	31	8.3%
	Nonspecific dermatitis	37	10%
	Lichen	21	5.6%
	Pseudolymphoma	7	1.9%
	Lupus	7	1.9%
	Parapsoriasis	5	1.4%
	Toxidermia	5	1.4%
	Other	85	22.9%
	MF confirmed histologically	57	15.4%

MF = mycosis fungoides.

patients (17.5%) (Fig. 5). Immunochemistry was positive for CD4 in 50 patients (87.7%), CD3 in 47 patients (82.4%), and CD30 in one patient (Table 2).

Univariate analysis results showed that psoriasiform and palmoplantar MF were the two clinical forms of MF that were easily misdiagnosed by clinicians and initially treated as psoriasis or eczema for an average of 10.5 years ($p = .003$). The delay in correctly diagnosing MF was a significant risk factor to develop an advanced stage of the disease (i.e., tumor or erythrodermic MF; $p = .009$).

In addition, we identified the following diagnostic criteria to distinguish MF from benign dermatosis: long disease duration, pruritus, deterioration of general condition, pigmented erythematous and erythematous scaly patches and plaques, lymphadenopathies, poikiloderma, nodules, tumors, erythroderma, leonine facies, depilation of the body, localization in hidden areas, scalp and nail involvement, ichthyosiform state, epidermotropism, Pautrier microabscess, superficial lymphoid infiltrate, clear cytoplasm (haloed cells), enlarged hyperchromatic cerebriform nuclei, and immunohistochemistry that is positive for CD4 and CD3 (Table 3).



Fig. 1. Clinical image of a psoriasisiform MF misdiagnosed as psoriasis.



Fig. 2. Clinical image of an eczematiform MF.

Discussion

MF is the most common, primary, cutaneous lymphoma and accounts for approximately 50% of cases (Burg et al., 2005; Willemze et al., 2005). The disease progresses slowly for years, evolving from erythematous patches on sun-protected skin to plaques and then to tumors and erythroderma. The clinical course generally remains indolent with disease-specific survival that approaches 90% (Willemze et al., 2005). However, disease prognosis and therapeutic options depend on the type of lesion (patch, plaque, or tumor), the extent of cutaneous involvement, and the presence of extracutaneous disease and large-cell transformation (Pimpinelli et al., 2005; Song et al., 2013; Willemze et al., 2005). In addition, the expected outcome and treatment options for patients with MF differ from patients with inflammatory mimics. For these reasons, accurate and early diagnosis of MF is essential.

However, in practice, the diagnosis of MF in an early stage can be very challenging because clinicopathologic findings overlap with various reactive and inflammatory dermatoses and conflict with clinical presentations and pathologic features. The histopathologic features of MF in an early stage vary from person to person, over time, and even between multiple sites in a single patient (Ferrara et al., 2008; Massone et al., 2005). In addition, topical steroid therapy and systemic immunosuppressant medications may influence the findings up to 2 to 4 weeks (Nickoloff 1988; Pimpinelli et al., 2005). These difficulties are highlighted by the false-negative and false-positive reporting rates, which can be as high as 40% (Herrmann et al., 1994), and the low concordance and reproducibility rates (Guitart et al., 2001; Olerud et al., 1992; Pimpinelli et al., 2005).



Fig. 3. Clinical image showing palmoplantar lesions of MF misdiagnosed as eczema.

Clinically, MF was mimicked by other biopsy-proven inflammatory diseases such as eczema, psoriasis, nonspecific dermatitis, lichen, lupus, pseudolymphoma, parapsoriasis, and toxidermia. This was confirmed by other studies that researched the overlapping histopathologic features of MF and psoriasis (Doukaki et al., 2009; Jinno et al., 2015), lichen (Citarella et al., 2003; Magro et al., 1997; Suchak et al., 2010), eczema (Ackerman et al., 1974; Ecker and Winkelmann, 1981; LeBoit and Epstein, 1990; Miyagaki and Sugaya, 2011; Orbaneja et al., 1976; Reddy and Bhawan, 2007; Solomon et al., 2016; White, 1990), pseudolymphoma (Choi et al., 2003; Rijlaarsdam et al., 1991, 1992), cutaneous drug reactions (Sarantopoulos et al., 2013), parapsoriasis (Goldberg, 2012), chronic and nonspecific dermatitis (Elmer and George, 1999), and others dermatosis (Deen et al., 2015; Fujimoto et al., 2015; Kazlouskaya et al., 2015; Lim et al., 2015; Rodriguez-Acosta et al., 2013; Yalcin et al., 2014).



Fig. 4. Clinical image of a poikilodermic MF.

Moreover, MF in an early stage is a great simulator because it shares common semiological characteristics with other inflammatory diseases, such as pruritus and erythematous scaly patches. This characteristic in addition to frequent self-medication could modify the appearance of the lesions. Also, MF may lack the typical clinical course, evolution, and characteristic histologic features; therefore, MF may be indistinguishable from other dermatoses such as eczema or psoriasis (Song et al., 2013).

Pathologic criteria alone may be insufficient and morphologic findings of MF in an early stage or lesions that were treated often

Table 2
Characteristics of study patients with MF

Characteristics	Number (57 Patients)	Percentage	
Age groups	≤15 years	0	0%
	15–45 years	18	31.5%
	≥45 years	39	68.4%
Gender	Female	30	52.6%
	Male	27	47.3%
Disease duration	≤5 years	8	14%
	5–10 years	33	57.8%
	≥10 years	16	28%
Pruritus		49	85.9%
Deterioration of general condition		15	26.3%
Erythematous plaques		17	29.8%
Erythematous scaly patches		28	49.1%
Papules		6	10.5%
Nodules		10	17.5%
Ulceration		3	5.3%
Pigmented patches		13	22.8%
Tumors		6	10.5%
Erythroderma		15	26.3%
Depilation of the body		7	12.3%
Poikiloderma		7	12.3%
Ichthyosiform state		1	1.8%
Localization in hidden areas		42	73.6%
Palmoplantar keratoderma		12	21.1%
Lymphadenopathies		24	42.1%
Scalp involvement		13	22.8%
Nails involvement		11	19.3%
Leonine facies		3	5.3%
Epidermotropism		51	89.4%
Pautrier microabscess		17	29.8%
Clear cytoplasm (haloed cells)		27	47.4%
Proliferation with big lymphocytes		6	10.5%
Proliferation with intermediate lymphocytes		21	36.8%
Proliferation with small lymphocytes		30	52.6%
Superficial lymphoid infiltrate		40	70.1%
Bandlike lymphoid infiltrate in superficial dermis		15	26.3%
Enlarged hyperchromatic cerebriform nuclei		10	17.5%
MF histological type	Classical MF	52	91.2%
	Folliculotropic MF	3	5.2%
	Transformed granulomatous MF CD30+	1	1.7%
	MF transformed into high grade CD30-	1	1.7%
Immunohistochemistry	CD4	50	87.7%
	CD3	47	82.4%
	CD30	1	1.7%

CD = cluster of differentiation; MF = mycosis fungoides.

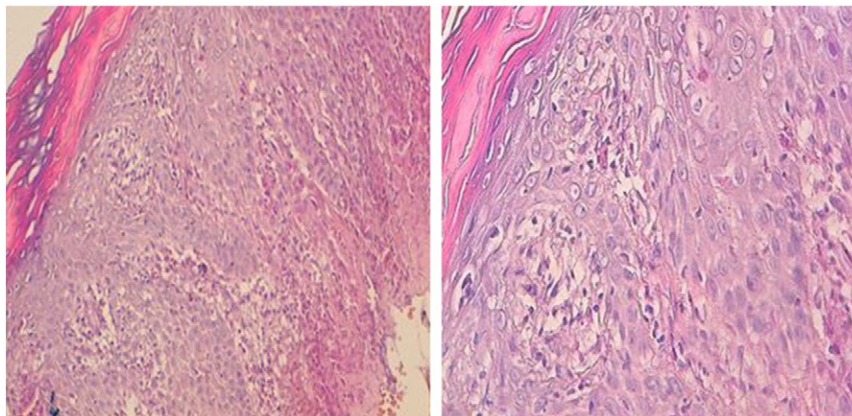


Fig. 5. MF at an early stage. Histologic features: epidermotropism, Pautrier microabscesses, superficial lymphoid infiltrate, clear cytoplasm (haloed cells).

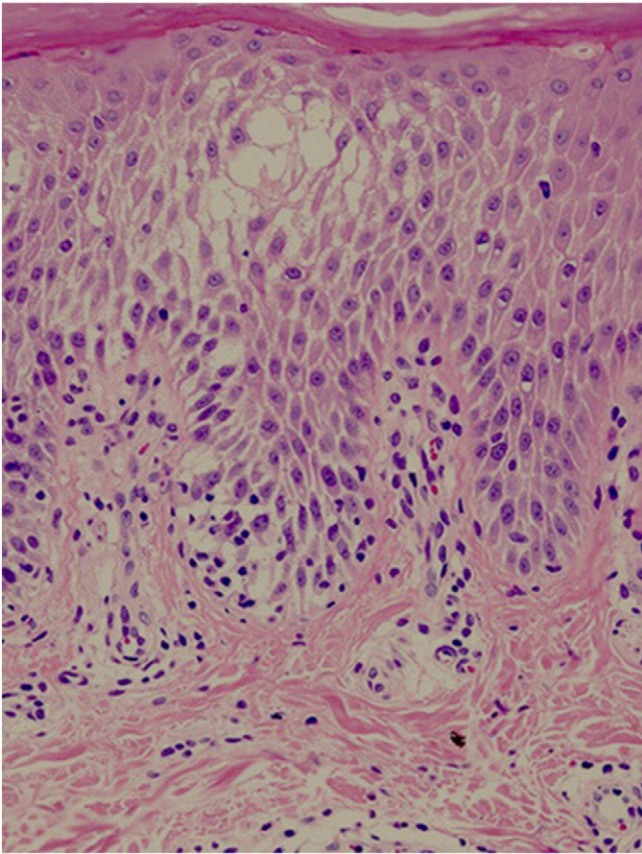


Fig. 6. Chronic eczema. Histologic features: disreet spongiosis with infiltration of the epidermis with lymphocytes (exocytosis).

show only minimal to mild epidermotropism without Pautrier microabscess. In addition, spongiosis, which is usually observed in patients with eczema, can be seen in approximately 30% of MF cases (Shapiro and Pinto, 1994). Therefore, the combination of the medical history, clinical information, and histopathology is crucial to avoid misdiagnoses.

In some cases, neither the clinical history nor the first biopsy specimen and T-cell gene rearrangement studies are helpful so close follow-up of the patient with repeated or multiple examinations of biopsy specimens from various lesions may be of help.

On the other hand, 84.5% of lymphoma cases that were diagnosed on the basis of clinical test results were subsequently excluded on the basis of histological test results. This may be due to the hospital doctors' fear of missing a diagnosis of MF, especially since this frequency in lymphoma is increased in addition to the absence of specific dermoscopic, biological, and/or radiological diagnostic signs. Thus, histology and immunohistochemistry have a place in the confirmation of the diagnosis.

In fact, we did not know whether MF was the first or final diagnosis, which can lead to confusion and complicate the pathologist's analysis and result in a misdiagnosis and patients who are untreated for years because of the initial benign appearance. Once the disease becomes systemic, the prognosis is significantly worse; therefore, it is crucial to specify the degree of certainty of the diagnosis that is mentioned by the clinician to guide the histopathologist and limit inconclusive skin biopsy test results.

Furthermore, because of these diagnostic challenges of MF in an early stage, we tried to describe the most reliable diagnostic criteria to distinguish MF from benign dermatoses. We defined criteria to help clinicians diagnose MF and confirm the diagnosis with a biopsy specimen test result. The criteria we defined are also beneficial to

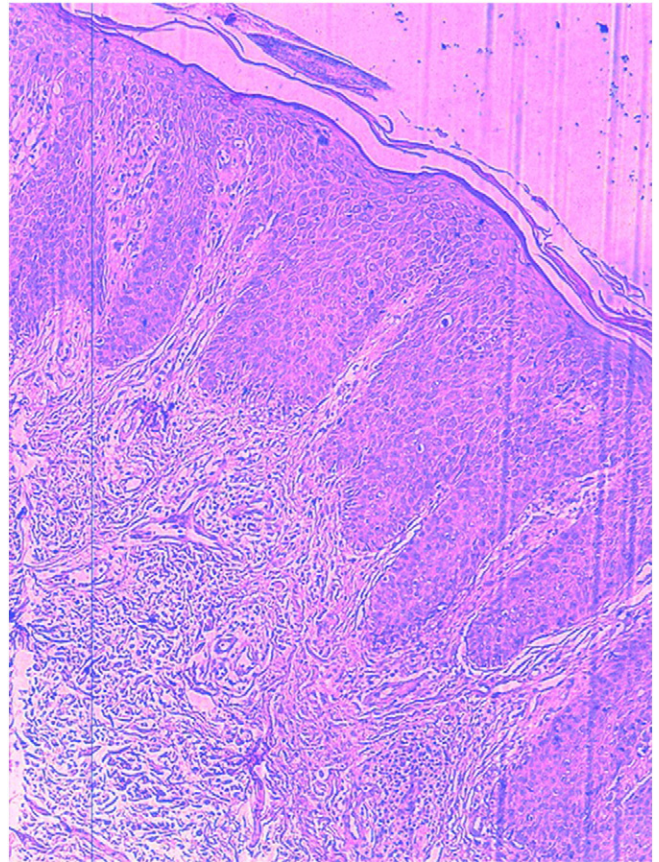


Fig. 7. Psoriasis. Histologic features: acanthosis, parakeratosis and orthokeratosis, loss of the granular cell layer and papillomatosis.

support and limit non-mandatory biopsies and are partially the same as those identified in 2005 (Pimpinelli et al., 2005) and 2015 (Vandergriff et al., 2015) by the International Society for Cutaneous Lymphoma. However, in our study, we did not include T-cell gene rearrangement studies.

Others studies focused on the histopathologic features of this correlation (Guitart et al., 2001; Nickoloff, 1988; Pimpinelli et al., 2005; Sanchez and Ackerman, 1979; Santucci et al., 2000; Shapiro and Pinto, 1994) and confirmed that the characteristic histopathologic

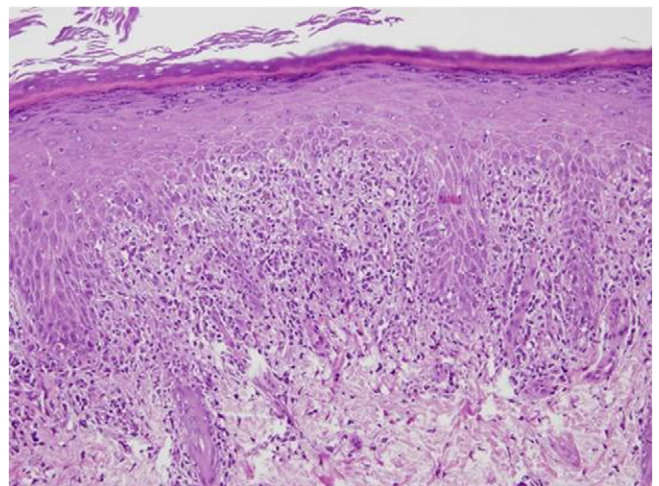


Fig. 8. Lichen planus. Histologic features: hypergranulosis, vacuolar Degeneration of the basal layer of the epidermis, Lymphocytic infiltrate of the superficial dermis and the dermoepidermal junction in a band-like pattern.

Table 3

Univariate analysis: characteristics that influenced clinicians to diagnose mycosis fungoides

Criteria	p Value
Long disease duration	.052
Pruritus	.000
Deterioration of general condition	.000
Plaque	.000
Ulceration	.000
Lymphadenopathies	.001
Pigmented patches	.000
Erythematous scaly patches	.000
Erythematous patches	.000
Depilation of the body	.0004
Poikiloderma	.000
Ichthyosiform state	.000
Nodules	.000
Tumors	.000
Erythroderma	.000
Localization in hidden areas	.000
Scalp involvement	.000
Nail involvement	.000
Leonine facies	.038
Epidermotropism	.000
Pautrier microabscess	.000
Clear cytoplasm (haloed cells)	.000
Enlarged hyperchromatic cerebriform nuclei	.000
Superficial lymphoid infiltrate	.003
Immunohistochemistry positive for CD4 and CD3	.001

CD = cluster of differentiation.

features of MF in an early stage include enlarged epidermal lymphocytes with cerebriform nuclei within the epidermis and epidermotropism, superficial lymphoid infiltrates, bandlike infiltrate in a thickened papillary dermis with coarse collagen bundles, lymphocytes with perinuclear clearing (halo), and a linear arrangement of boiler epidermal lymphocytes along the dermal-epidermal junction (i.e., tagging; Santucci et al., 2000). However, none of these features are entirely specific for MF. Even though the pattern may vary, epidermotropism is considered a hallmark of MF and has been reported in up to 96% of patients with MF in an early stage (Massone et al., 2005). In our study, epidermotropism was present in 89.4% of patients.

Pautrier microabscess is considered more specific for MF but is only seen in 4% to 37% of lesions in an early stage (Burg et al., 2005; Massone et al., 2005; Naraghi et al., 2003; Santucci et al., 2000; Shapiro and Pinto, 1994) and in 29.8% in our study. In some cases, atypical lymphocytes in MF may be associated with spongiosis but the degree is usually far less than would be expected for the number of lymphocytes in the epidermis, a feature that is sometimes called disproportionate epidermotropism (Massone et al., 2005; Pimpinelli et al., 2005; Sanchez and Ackerman, 1979).

Also, the loss of pan-T-cell markers (CD2, CD3, CD5, and CD7) and a marked dominance of CD4 or CD8 favor a diagnosis of MF, particularly if those findings are seen in epidermal but not dermal lymphocytes (Bergman et al., 1998; Burg et al., 2005; Ortonne et al., 2003; Pimpinelli et al., 2005). Importantly, reactive processes may show loss of T-cell markers, most commonly in CD7 and CD5 (Magro et al., 2003; Michie et al., 1990; Murphy et al., 2002; Regauer and Beham-Schmid, 2006; Rijlaarsdam et al. 1992; Suchak et al., 2010), but the loss of these markers in inflammatory conditions is often less extensive than in MF (Pimpinelli et al., 2005; Wood et al., 1986). In addition, many inflammatory dermatoses show a near-equal mixture of CD4+ and CD8+ T-cells or only a mild predominance (Murphy et al., 2002; Ortonne et al., 2003; Rijlaarsdam et al., 1991, 1992; Suchak et al., 2010) so this generalization is far from universal (Magro et al., 2003). As a result, awareness of the variable appearances of MF in an early stage is important to appropriately diagnose in these challenging cases.

Despite the continued refinement of histologic criteria to diagnose MF in an early stage, the diagnosis is best made with a combination of clinical history data and histopathologic, immunophenotypic, and sometimes genetic findings, which are not always helpful or available. This is why the pillar of a diagnosis of MF, especially in an early stage, is best supported by a combination of findings from both a clinician and a pathologist.

Conclusion

In our study, we found that psoriasis, eczema, and other skin diseases may mimic MF, especially in an early stage of the disease. We also defined significant diagnosis criteria for MF to limit unnecessary biopsies and increase diagnosis specificity.

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