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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 psoriasiform 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.

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 ± 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 treated 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 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).

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.

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).

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