original article

Profile of mycosis fungoides in 43 Saudi patients

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Ann Saudi Med 2012; 32(3): 283-287

DOI: 10.5144/0256-4947.2012.283

BACKGROUND AND OBJECTIVES: Mycosis fungoides (MF) is a rare disease; and to our knowledge, there are no reports on its profile in Arabs. The objective of this study was to preliminarily analyze the clinical characteristics of MF patients seen in our institution.

DESIGN AND SETTING: Retrospective review of 140 patients with pathologic or clinical diagnosis or differential diagnosis of MF for the period 2000-2006.

PATIENTS AND METHODS: Pathology reports with diagnosis or differential diagnosis of MF were retrieved and suspected cases were identified and reviewed. For pathologically confirmed cases, sociodemographic, clinical, laboratory, and radiological details were collected. Details of staging, treatment modalities, and disease status at the last follow-up were retrieved.

RESULTS: A total of 43 pathologically confirmed MF patients (skin phototypes IV and V) with a mean age at diagnosis of 33.5 years were reviewed. This comprised 29 males (M:F ratio, 2:1), and the majority (86%) of patients had early-stage (I and II) MF. Twenty-one (48.8%) patients had classic MF; 18 (41.8%), hypopigmented MF; and 4 (9.3%), other variants. The male-to-female ratio was higher in the hypopigmented (3.5:1) than in the classic variant (1.6:1). The mean age at diagnosis was lower in the hypopigmented compared to the classic variant (25 versus 38.8 years, *P*=.019). The mean duration of follow-up was 27.6 months (range, 1-98 months). At the final assessment, 4 (9.5%) patients recovered; whereas 35 (83.3%) had MF skin disease; 1 had (2.4%) extracutaneous disease; and 2 (4.8%) died of MF.

CONCLUSIONS: MF tends to affect younger Saudi patients. The hypopigmented variant constitutes a significant proportion of MF cases, especially in younger patients.

Cutaneous T-cell lymphoma (CTCL) is a peripheral non-Hodgkin T-cell lymphoma characterized by skin-homing lymphocytes.[1,2] Mycosis fungoides (MF) was first described in a case report by the French dermatologist Alibert in 1806.[3] It is the most common type of CTCL and is the second most common site of extranodal non-Hodgkin lymphoma, accounting for 7% to 18% of all malignant lymphomas.[4] No reports are available describing clinical features of MF in Arabs. Moreover, we observed that in our population, MF tends to occur at a younger age as compared with the international figures.[5] Therefore, our aim here was to analyze the details of MF in our institution and compare them with international data. Therefore, we decided to review all of the MF cases diagnosed during the period 2000-2006 in the King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia.

PATIENTS AND METHODS

After approval by the ethical review board of King Khalid University Hospital, King Saud University, Riyadh, we performed a retrospective review of 140 patients with pathologic or clinical diagnosis or differential diagnosis of MF for the period 2000-2006. Skin biopsies were reviewed by two dermatopathologists (M. Arafah and A. Ajlan). All cases of clinical correlation with pathologic confirmation of MF (43 cases) were included in this study. A chart review was performed, and sociodemographic data and all clinical details were collected. We also retrieved details of investiga-

Table 1. Demographic profile and clinical findings of 43 Saudi patients with mycosis fungoides.

Demographic profiles	Value
Sex	
Male, number (%)	29 (67)
Female, number (%)	14 (33)
Male-to-female ratio	2:1
Age at diagnosis	
Mean, years	33.5
Median, years	30.5
Range, years	5-74
Duration of symptoms	
Mean, months	88
Median, months	60
Range, months	2-360
Duration of follow-up	
Mean, months	27.6
Median, months	24
Range, months	1-98
Clinical findings	
Types of mycosis fungoides (n=43)	
Classic, number (%)	21 (48.8)
Hypopigmented, number (%)	18 (41.8)
Others,[a] number (%)	4 (9.3)
Staging (n=30, missing=13)	
Ia, number (%)	13 (43.3)
Ib, number (%)	10 (33.3)
IIa, number (%)	2 (6.7)
IIb, number (%)	1 (3.3)
III, number (%)	2 (6.7)
Iva, number (%)	0 (0)
Ivb, number (%)	2 (6.7)

[a]One erythrodermic, 1 hyperkeratotic, and 2 poikilodermic cases.

tions, including the number of skin biopsies, complete blood count (CBC), Sézary cells, lactate dehydrogenase (LDH), liver function tests (LFTs), uric acid, chest x-ray (CXR), chest computed tomography (CT) , abdominal CT, lymph node biopsy and bone marrow biopsy. Moreover, details of staging, treatment modalities used, and disease status at the last follow-up were collected. The number of biopsies required for establishing the diagnosis and the initial differential diagnoses were also documented where applicable.

In general, the diagnosis of classical MF and its variants was based on characteristic clinical and histological features, such as the presence of persistent or progressive erythematous or poikilodermatous patches or plaques in mainly sun-protected areas together with histological findings of a band-like superficial atypical lymphoid infiltrate with epidermotropism.[6] All statistical analyses were performed using SPSS 12.0 (IBM Corp, Armonk, NY, USA). Associations were determined by the Pearson chi-square test or the Fisher exact test. Statistical significance was set at $P<.05$.

RESULTS

A total of 43 patients (skin phototypes IV and V), all cases of clinical correlation with pathologic confirmation of MF, were reviewed. **Table 1** summarizes the demographic profile of all patients. Twenty-one (48.8%) patients were 30 years of age or younger at diagnosis, whereas 21 (48.8%) were 31 years of age or older (age missing in 1 case). No statistical difference was observed in the mean age at diagnosis between male and female patients. The mean duration from appearance of the first symptoms and signs to confirmation of the diagnosis was 7.4 years (median, 5 years). No family history of lymphoma or skin cancer in any of our patients was reported. None of the patients had HIV or other forms of immunosuppression.

Clinical features are summarized in **Table 1**. The lesions in 20 (46%) out of 43 patients were non-itchy. Twenty-one (48%) patients presented with classic MF (patch, plaque and/or tumor). The mean body surface area affected by MF was 20.2% (median, 9%; range, 1%-100%). Twelve (31.6%) patients had palpable lymph nodes; of these patients, 6 (54.5%) underwent lymph node biopsy, which was negative. One (3%) patient had organomegaly. In 11 (28.2%) patients, the disease initially presented as eczema. An initial diagnosis of psoriasis, parapsoriasis, and pityriasis lichenoides was reported in 6 (14%), 6 (14%), and 4 (9%) patients, respectively. With regard to hypopigmented MF, 7 (39%) cases out of 18 were diagnosed initially as either vitiligo or pityriasis alba.

The mean duration of follow-up was 27.6 months (median, 24 months; range, 1-98 months). The mean number of skin biopsies needed for the diagnosis of MF was 1.76 (median, 2; range, 1-3). Laboratory results showed that 2 (5%) patients had abnormal CBC with a high eosinophil count. Circulating Sézary cells were ab-

sent in all the 7 patients tested. Five (13.2%), 3 (7.5%) and 2 (5.1%) patients had abnormal LDH, LFTs, and uric acid, respectively. Levels of urea and electrolytes were normal for all patients. One (2.6%) patient had an abnormal chest x-ray in the form of calcified lymph node in the paratracheal region; 2 (5.1%) patients had an abnormal CT chest (1 patient had bilateral axillary lymph node enlargement and the other had enlarged bilateral lower cervical lymph nodes); 2 patients had abnormal pelvis CT (both in the form of bilateral inguinal lymph node enlargement); 2 patients had an abnormal abdominal ultrasound (both showed hepatomegaly); and 3 (7.5%) patients had an abnormal abdominal CT (all showed hepatomegaly). Bone marrow biopsy was normal in 5 (12.2%) patients. The mean duration of follow-up was 26.7 months (median, 24 months; range, 1-132 months).

At the last follow-up, 11 (28.9%) patients showed improvement, 18 (47.4%) patients showed deterioration, and 9 (23.7%) patients had no change in the disease status. Four (9.5%) out of 43 patients recovered, 35 (83.3%) patients still had MF skin disease, 1 (2.4%) patient had extracutaneous MF disease, and 2 (4.8%) patients died of MF (secondary to visceral organ involvement).

Table 2 summarizes the characteristics of the patients stratified to the main MF variants. Males marginally outnumbered females in classic MF group (13 out of 21 patients). However, the majority (78%) of patients in the hypopigmented MF group were males (14 out 18) (P=.018). The mean age at diagnosis was lower in hypopigmented MF patients as compared to classic MF patients (25 vs. 38.8 years, P=.019). Thirteen (72%) out of 18 patients with hypopigmented MF were 30 years of age or younger at diagnosis. Seven (33%) out of 21 patients with classic MF were 30 years of age or younger. The majority of cases were in early stages (I and II) in both classic MF (12 out of 15, 80%) and hypopigmented MF (11 out of 11, 100%). **Table 3** summarizes the different treatment modalities used. Eight (22.9%) patients had complete remission, 17 (48.6%) patients had partial remission, and 10 (26.6%) patients had no response to the treatment.

Table 2. Clinical characteristics of 43 Saudi patients with mycosis fungoides.

Clinical characteristics	Classic MF (n=1)	Hypopigmented MF (n=18)	Others[a] (n=4)
Sex			
Male	13	14	2
Female	8	4	2
Male-to-female ratio	1.6:1	3.5:1	1:1
Age at diagnosis			
Mean, years	38.8	25	44.7
Median, years	36.5	22	40
Range, years	15-60	5-59	25-74
Staging	**(n=15, missing=6)**	**(n=11, missing=7)**	**(n=4)**
Ia	7	4	2
Ib	3	6	1
IIa	1	1	0
IIb	1	0	0
III	1	0	1
IVa	0	0	0
IVb	2	0	0

MF: Mycosis fungoides. [a]One erythrodermic, 1 hyperkeratotic and 2 poikilodermic cases.

Table 3. Treatment modalities used for mycosis fungoides in 43 Saudi patients.[a]

Treatment modality	Number (%)
Topical corticosteroids	22 (51.2)
Narrow-band UVB (NBUVB)	21 (48.8)
Oral psoralen plus UVA (PUVA)	6 (14)
NBUVB and acetretin	9 (20.9)
PUVA and acetretin	1 (2.3)
Chemotherapy (systemic)	2 (4.7)
Others	10 (23.3)

[a]Many patients had more than one treatment modality at different periods of their disease.

DISCUSSION

To the best of our knowledge, this is the first report on the profile of MF in Arabs, in which we have described 43 cases of MF with skin phototypes IV and V. Half of them were 30 years of age or younger. Moreover, the majority of patients had an early-stage disease. Overall, MF is a rare disease. The annual incidence of MF is 0.5 per 100 000 population in the Netherlands; whereas the estimated incidence rate of MF in the USA is 0.36 per 100 000 person-years.[7] In Singapore, the annual incidence of MF is estimated to be at least 0.62 per 100 000 population. However, due to the lack of local statistics, we do not know the incidence of MF in Arab countries. In our study, we found an overall male predominance, with a 2:1 male-to-female ratio, which

is consistent with other studies from the USA, the Netherlands, Hong Kong, and Singapore.[8,9]

We found an earlier onset of MF in our population, with a mean age of 33.5 years at diagnosis (median, 30.5 years). Patients who were 30 years of age or younger constituted 50% of our study population. This high percentage of young MF patients is inconsistent with the corresponding percentage figures found in the available published reports, in which MF is reported to occur predominantly in older adults, most commonly in the fifties. In the Stanford study, the median age at presentation was 57 years, comparable to the median age at diagnosis of 61 years in a Dutch review of 309 patients.[8,9] In Asia, the median age at diagnosis was 64.3 years in a Japanese study and 53 years in a Hong Kong report.[10] Hypopigmented MF has been described in children,[11] especially in those with dark skin; and for unknown reasons, it has an unusually high frequency in this age group.[12] Hypopigmented MF may be mistaken for a variety of benign entities, including vitiligo, or pityriasis alba.[13]

Vitiligo is frequently confused with hypopigmented MF in patients with a dark complexion. Several features have been described to distinguish both. Vitiligo manifests as depigmented macules due to the absence of melanocytes and melanin pigment. However, hypopigmented MF presents as hypopigmented macules, which is due to the partial loss of melanocytes and melanin. Moreover, epidermotropism, hydropic degeneration of basal layer, preservation of some melanocytes, dermal fibrosis, and presence of lymphocytes in papillary dermis are seen more in hypopigmented MF in comparison with vitiligo. The loss of pigmentation in hypopigmented MF is probably due to the cytotoxic effects of CD8 cells on melanocytes.[14] The high frequency of hypopigmented MF in children emphasizes the need to consider MF as a differential diagnosis of chronic hypopigmented dermatoses for early diagnosis of the disease.[12] The high incidence of hypopigmented MF (42%) in our study group may attribute to the younger age of our patients. Nevertheless, patients with classical MF had a mean age of 39 years, which is younger than the mean ages reported in a majority of other studies. The only exception is a single study from Singapore that showed a younger age at diagnosis (mean, 33 years).[15] The younger age in our patients could be explained by a high proportion of the hypopigmented variant (42%), which is known to occur more in younger patients.[15] Moreover, we might be diagnosing MF earlier because of a close follow-up with serial biopsies if the patient is clinically suspected to have MF.

It is worth noting that the hypopigmented variant made up almost 42% of our study population. Similarly, in a recent retrospective study from Singapore, 47 (36%) out of 131 MF patients had the hypopigmented variant.[15] In a previous study by Tan et al on childhood MF, 8 of the 9 patients presented with the hypopigmented variant.[16] Other studies from Singapore showed the hypopigmented variant in 45% of their study group. An association between hypopigmented MF and young age has previously been reported in the published work.[16] In our study, 39% of hypopigmented MF cases were initially diagnosed as vitiligo or pityriasis alba. As proposed by Tan et al, it is likely that the earlier stage of presentation and predominance of hypopigmented MF variant seen in their study (as well as in our study) are attributable to the relative ease of detection of hypopigmented lesions in darker skin.[15]

Our analysis of individual disease variants revealed several interesting observations. In hypopigmented MF, the most striking feature was that of male predominance; which is different from the Singapore study,[15] showing the absence of any sex predilection. However, classic MF showed a male predominance (1.6:1), which is much lower than that showed in the Singapore study (4.2:1).[15] Most of our patients with classic and hypopigmented MF presented at an early stage of the disease (I and II), which is consistent with other studies.[15] The early diagnosis of MF is challenging, with a reported median duration of symptoms at presentation of approximately 50 months,[8] which is similar to our finding (60 months).

A limitation of this study is that in a chronic relapsing disease like MF, which runs over years or even decades, this 7-year retrospective cohort review permitted only a relatively short follow-up duration (mean, 2.3 years) among our patients, whose long-term disease status could not be addressed by the present study.

Although MF is a rare disease, it is important to have a high index of suspicion. It is also particularly interesting that we found a significant proportion of MF to be of the hypopigmented variant, especially among the younger age group. This variant was associated with a good outcome because all cases presented with an early stage of the disease. This diagnosis should be carefully considered in any young dark-skinned patient presenting with persistent hypopigmented patches, especially over the trunk and sun-protected areas.

Despite the fact that MF is usually described as pruritic, pruritus was absent in 50% of our patients.[17] A nonpruritic nature is therefore a symptom that can help to differentiate between MF and eczema, a condition for which early MF is commonly mistaken. Clinically, MF can be confused with many inflammatory skin dis-

eases. In our study, a proportion of patients were initially diagnosed with eczema (28%), psoriasis (14%), parapsoriasis (14%), or pityriasis lichenoides (9%).

Clinicopathologic correlation remains the gold standard for the diagnosis of MF, despite the advent of ancillary tools such as gene rearrangement studies. The diagnosis of early MF is often difficult. It took our physicians an average of 88.8 months (median, 60 months) from the onset of symptoms to give the correct diagnosis. In the published report, the corresponding mean and median values are 73.2 and 48 months, respectively.[18] It has been demonstrated that when histologic findings alone are used, the false-negative and false-positive rates are as high as 40% and 44%, respectively, for the diagnosis of early MF.[19] MF can mimic almost any inflammatory skin disorder histologically.[20] Therefore, repeat biopsies with clinical correlation are necessary to confirm the diagnosis.

The overall mortality rate in the present study was 4.8% (2 out of 43 patients). The majority of MF patients show an indolent clinical course over years to decades.[21] The prognosis of the disease is defined by its stage. Patients with early stages have an excellent prognosis with survival similar to that of an age-, sex-, and race-matched population.[22] Factors indicating poor prognosis are advanced stage and age above 60 years.[23] When extracutaneous involvement or transformation into high-grade lymphoma occurs, expected survival is usually less than 1 year.[24]

To summarize, this is the first report describing the profile of MF in Saudi patients. MF is a rare disease that needs a high index of suspicion with repeated skin biopsies to be diagnosed. In our cases, MF tended to affect patients of a younger age as compared to international figures. Hypopigmented variants made up 42% of our MF cases. Male predominance and younger age were striking in this variant. Any persistent hypopigmented patches, especially over the trunk and sun-protected areas, in young dark-skinned patients need to be taken seriously and biopsied early not to miss MF diagnosis.

Acknowledgments

Authors would like to thank the College of Medicine Research Center and Vitiligo Research Chair, King Saud University, for supporting this study. Dr. Abdul-Aziz Al-Ajlan, consultant dermatopathologist, reviewed all histologic slides.

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