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Morphological Pattern of Mycosis Fungoides Among Saudi Patients Attending King Abdulaziz University Hospital

King Abdulaziz Üniversitesi Hastanesi'ne Başvuran Hastalar Arasında 'Mikozis Fungoides'in Morfolojik Paterni

Abstract

Objective: This study was performed to determine the morphological pattern of MF among Saudi patients at King Abdulaziz University Hospital, Jeddah, Saudi Arabia.
Methods: The analysis included 151 skin cancers with a histological diagnosis among Saudi patients between Jan 1995 and Dec 2012. Morphological pattern of MF by age, sex , anatomic location, histological and immunohistochemical features was examined.
Results: MF accounted for 12.5%of all histologically diagnosed cases of skin cancer among Saudi patients.It ranked as the third skin cancer in the order of frequency with a mean age of 44.6 years and male predominance. The most frequent sites of distribution were the thighs followed by legs and the most frequent histological type was the early or patch type. The atypical lymphocytes showed CD 3 expression in all cases with immunohistochemical studies.CD4 was positive in 26.6% while all cases were negative for CD 20.
Conclusion: In conclusion, MF is a rare tumor and ranked third in frequency of skin cancers among Saudis showing predilection for younger males which highlights the ethnic and/or regional variation in the clinico-epidemiological characteristics of MF

Key words: Mycosis fungoides, epidermotrophic lymphocytes, younger males, CD 3

Özet

Amaç: Bu çalışma King Abdulaziz Üniversitesi Hastanesi'ne (Cidde, Suudi Arabistan) başvuran Suudi hastalar arasındaki MF paternini saptamak amacıyla gerçekleştirildi.
Yöntemler: Çalışmaya Ocak 1995-Aralık 2012 tarihleri arasında histolojik tanılı deri kanseri olan 151 Suudi hasta dahil edildi. Yaş, anatomik lokalizasyon, histolojik ve immünohistokimyasal özelliklere göre MF'nin paterni incelendi.
Bulgular: Histolojik tanılı deri kanseri olan Suudi hastalar arasında MF oranı %12.5 idi. Sıklık sırasına göre üçüncü deri kanseri idi ve ortalama yaş 44.6 olup erkek hakimiyeti vardı. En sık dağılım bölgesi uyluk olup bunu bacaklar takip ediyordu ve en sık histolojik tipi erken ya da yama tipi idi. İmmünohistokimyasal çalışmalar ile tüm vakalarda atipik lenfositlerde CD3 ekspresyonu gösterildi. CD4 %26.6'sında pozitif iken, CD20 açısından tüm vakalar negatif idi.
Sonuç: Sonuç olarak, MF nadir bir tümördür ve Suudiler arasında deri kanserleri arasında üçüncü sıradadır. Genç erkekleri tutma eğiliminde olması MF'nin kliniko-epidemiyolojik özellikler açısından etnik ve/veya bölgesel değişkenliklerini göstermektedir.

Anahtar kelimeler: Mikozis funguides, epidermotrofik lenfositler, genç erkekler, CD3

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Introduction

Cutaneous lymphomas is a large group of diseases with a wide range of clinical and histologic variants exhibiting infiltration of the skin by malignant lymphocytes. Approximately two-thirds of these lymphomas are of T-cell origin. The most common form of cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF) (1). Se´zary syndrome (SS) is much rarer (1). The estimated annual incidence rate in the United States is only approximately 0.64 per 100,000, or fewer than 1000 new cases diagnosed each year showing an increase in frequency compared to the past (2). It accounts for only 2%of new cases of non-Hodgkin lymphoma. It is distinguished from other CTCLs by its unique clinicopathologic features (2). It commonly affects older adults (median age 55 to 60 years); however, it may affect younger individuals (2,3). The male to female ratio is 2:1 with male predominance (2,3). Clinically, patients present with pink red scaly patches and plaques, and eventually tumors that typically occur on sun-protected skin (breast, axilla, and buttocks being the most common sites) (4,5). The most common presentation is one of patches and plaque (4,5).

MF is one of the most difficult diagnoses to make in dermatopathology because of a highly variable number of clinical presentations and the sometimes nonspecific nature of the histologic findings (5). MF is a great masquerader and its distinction from an inflammatory condition such as chronic eczema and psoriasis is extremely difficult (5,6). The other reason is the heterogeneity of presentation and the lack of highly characteristic immunophenotypical and genetic markers (7).

MF is a relatively rare cancer in this region leaving the literature very deficient on the pattern of MF in Saudi Arabia and as such this study was undertaken to enhance our knowledge regarding this disease.

This study was performed to determine the morphological pattern of MF among Saudi patients at King Abdulaziz University Hospital, Jeddah. Pattern of MF by age, sex, anatomic location, histological features and immunohistochemical expression was examined.

Methods

Study Setting and Population

Initially all histopathologically diagnosed skin cancer cases among Saudi patients were retrospectively identified in the period between January 1995 and December 2012. Cases included all biopsies, excisions and referrals. The cases were identified through a computerized data base search of the Anatomic Pathology departmental archives at King Abdulaziz University, Hospital (KAUH) Jeddah. In the second step the data targeting all clinically diagnosed and histopathologically confirmed cases of MF among Saudi patients was isolated.

Table 1. Age and sex distribution of Mycosis Fungoides among Saudi patients at King Abdulaziz University Hospital Jeddah, Saudi Arabia

Total n=19	Less than 20 yrs		20-39 yrs		40-59 yrs		60-79 yrs	
	M	F	M	F	M	F	M	F
	-	-	7	1	9	3	1	1
%	-	-	36.8	5.2	47.3	15.7	5.2	5.2

Clinical and histopathological case definition of MF used was based on the scoring criteria of meetings of International Society for Cutaneous Lymphoma (8). Clinical definition included persistent and/or progressive patches/ thin plaques more than 5 cm in diameter occurring in non-sun exposed location. Histopathological criteria used were the presence of atypical lymphoid cells that are slightly larger than normal lymphocytes and have hyperchromatic, irregularly contoured (convoluted) nuclei, presence of individual haloed atypical lymphocytes within the epidermis, presence of single lymphoid cells linearly arranged along the basal layer of the epidermis presence of an increased number of lymphocytes (not necessarily atypical) relative to typical dermatitis, distributed singly or in small collections perivascularly in epidermis or presence of papillary dermal fibrosis (8).

Data Collection

Target data was collected using most appropriate Systematized Nomenclature of Human Medicine (SNOWMED) morphologic codes, and cases were divided according to gender, age groups and location. Other parameters such as date of receiving biopsy, personal identity (Medical record number, age, sex, nationality) clinical diagnosis, morphology, topography etc were also included. The data was manually cross checked to delete repetitions of cases such as recurrences. Computerized search was then transferred to Microsoft Excel format and used for statistical analysis. The age, gender and site related correlation was evaluated. Manual review of biopsy reports was completed twice independently and discordance, if any, was resolved through a third check.

All cases were processed as per standard histopathological techniques which include paraffin embedding and Hematoxlyin and Eosin staining. Microscopic examination was done twice on separate occasions to overcome diagnostic bias. Immunohistochemical staining using an automated stainer with the avidin-biotin-peroxidase

Table 2. Location of lesions in Mycosis Fungoides among Saudi patients at King Abdulaziz University Hospital Jeddah, Saudi Arabia

Location	Number of cases	Side	%n =19
Upper extremities Arm	2	1 right 1 left	10.5
Hand	1	1 right	5.2
Lower extremities Thigh	7	6 right 1 left	36.8
Leg	6	right	31.5
Heel	1	right	5.2
Foot	1	left	5.2
Abdomen	1		5.2
Back	2		10.5
Chest	1		5.2

Table 3. Histopathological and immunohistochemical features of Mycosis Fungoides among Saudi patients at King Abdulaziz University Hospital Jeddah, Saudi Arabia

Histological Features	Number of cases N=19	%N
EPIDERMAL CHANGES		
Architecture of atypical lymphocytic infiltrate		
Patchy	17	89.4
Lichenoid	2	10.5
Pattern of atypical lymphocytic infiltrate		
Epidermotropism	6	31.5
Clustered cells(Pautrier abscess)	3	15.7
Lymphocytes within spaces	1	5.2
Basal single cell infiltration	5	26.3
Other features		
Psoriasiform hyperplasia	2	10.5
Acanthosis	2	10.5
Spongiosis	5	26.3
Atrophy	1	5.2
Hyperkeratosis	4	21
Parakeratosis	2	10.5
Dermal Changes		
Coarse fibrosis of papillary dermis	3	15.7
Perivascular atypical lymphocytic infiltrate	5	26.3
Chronic Inflammatory cells other than lymphocytes	4	21
Involvement of skin appendages	3	15.7
Melanin incontinence	3	21
Cytological Features		
Small to medium sized cells	19	100
Hyperconvoluted nuclei	12	63.1
Perinuclear halos	9	47.3
Atypical mitosis	4	21
Immunohistochemical expression	N=15	%N
LCA positive	15	100
CD3 positive	15	100
CD4 positive(n=5)	4	80
CD5 positive	3	13.6
CD 8 positive	2	9
CD20 negative	15	100
CD 30 negative (n=8)	8	100

Table 4. a) Analytical comparison with other national studies

MF	This study	Arafah M et al. Riyadh S[13]	AlGhamdi KM et al. Riyadh S[14]	Akhtar SS et al. Qassim S[15]
MF n=	19	58	43	5
Mean age	44.6	5-70	33.5	33
M: F ratio	3:1	1.9:1	2:1	0.6:1

MF: mycosis fungoides, M: male, F: female

Table 4. b) Analytical comparison with other international studies

MF	This study	LS Ku and KK Lo Hong Kong[16]	Alsaleh QA et al. Kuwait[19]	F Naeini et al. Iran[20]	Haddadin WJ Jordan 21	Castella A et al. UAE[22]
MF n=	19	40	193	18	10	2
Mean age	44.6	56.4	35.5	41.6	48.5	62
M: F ratio	3:1	2:1	2:1	1:1	7:3	1:1

MF: mycosis fungoides, M: male, F: female

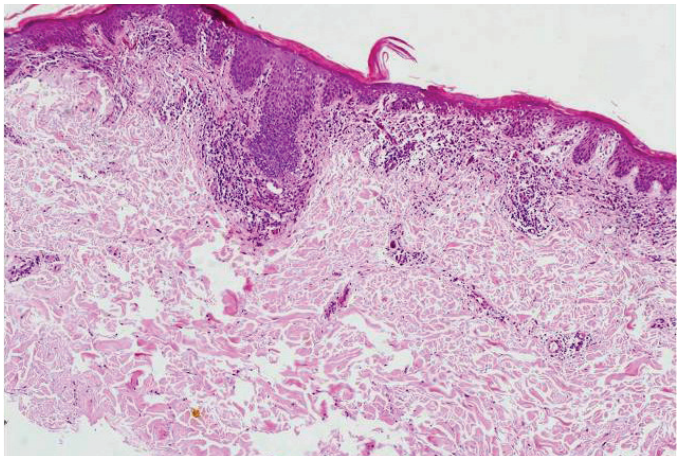

Figure 1A. Histologic section from early lesion showing hyperkeratosis, parakeratosis with superficial lymphoid infiltrate along the dermoepidermal junction and dermal fibrosis

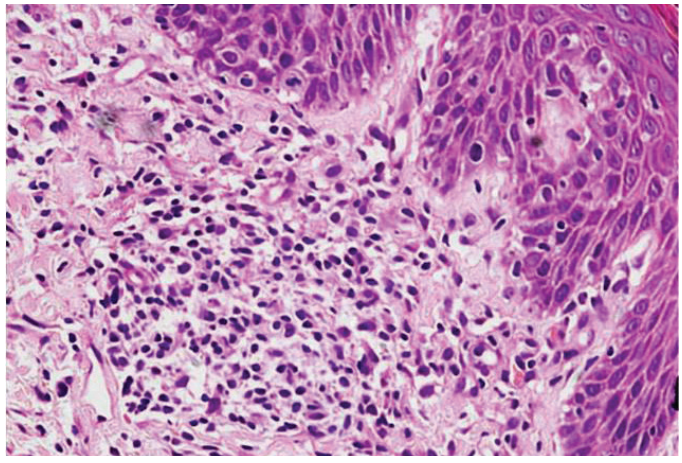

Figure 1B. Higher magnification revealed that the infiltrate was epidermotropic and was composed of small to intermediate lymphocytes exhibiting halos

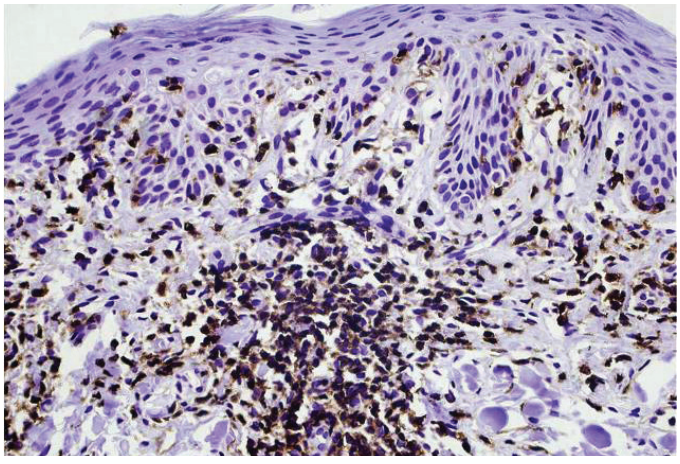

Figure 1C. LCA.Epidermotropism and hyperconvoluted atypical lymphocytes in superficial dermis

complex method was performed in 15 cases using the antibodies such as Leucocyte common antigen (LCA), CD 4, CD 3,CD5,CD 8,CD 20 and CD30 which were available as ready to use kits (Ventana,Rocklin, CA, USA). Antibodies were used to highlight the atypical lymphocytic components. Results were scored as follows: -, not seen; +/-, rare/focal positivity; +, diffuse positivity. Positive and negative controls were performed for the stain. In the remaining cases immunohistochemical studies were compromised by the tiny nature of the biopsy material submitted or by the availability of resources. Clinical data were obtained from the patients' hospital records. Diagnosis was based on the clinical data combined with the histopathologic and immunohistochemical findings of MF.

Literature reviews including epidemiological studies, case reports, and diagnostic articles about MF analyzed in the English literature from 2000-2012 through the national library of medicine, Pubmed and OVID medline search engines. Keywords used were "cutaneous T cell lymphoma", "mycosis fungoides", "epidemiology", "pattern of mycosis fungoides".

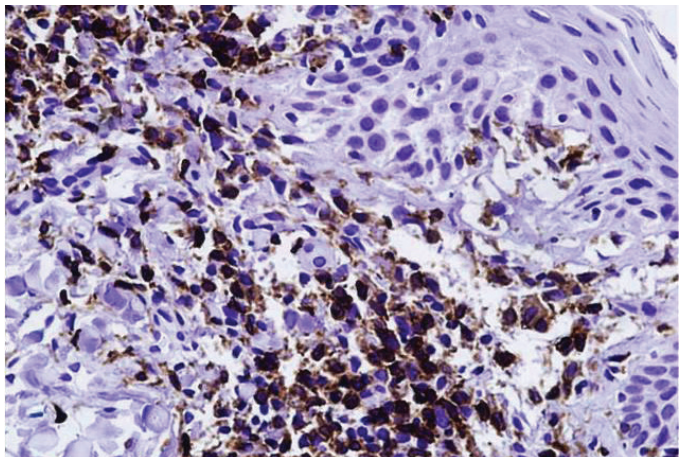

Figure 1D. CD3 Positivity in the atypical superficial dermal and epidermotrophic lymphocytic infiltrate.

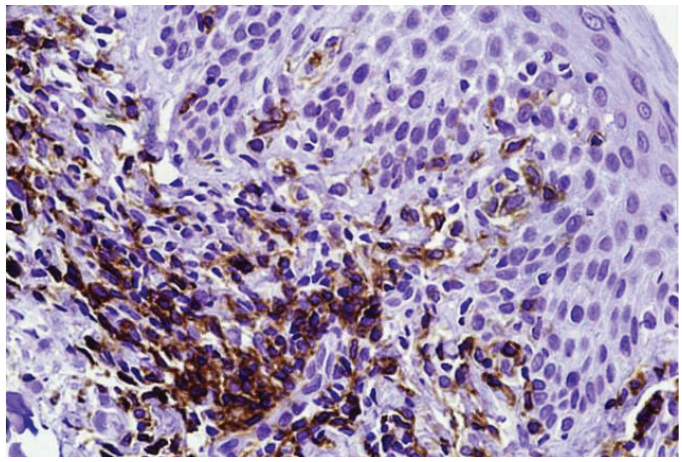

Figure 1E. CD4 Positivity in the atypical superficial dermal and epidermotrophic lymphocytic infiltrate.

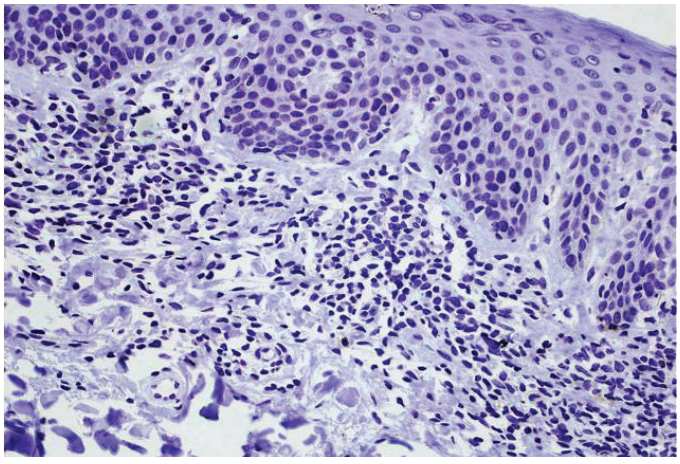

Figure 1F. CD 20.Negativity in the atypical superficial dermal and epidermotrophic lymphocytic infiltrate.

Statistical Analysis

Data were analyzed using the program Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA).

Descriptive and frequency statistics were obtained for the variables studied. Statistical significance was set at $p<.05$. The procedures followed in the present study were in accordance with the ethical standards of the hospital ethical committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Results

There were 151 cases of skin cancer among Saudi patients attending KAUH, Jeddah. The mean age of all cases was 49 years. The most common skin cancer was basal cell carcinoma (28.4%) with a mean age of 66 years followed by squamous cell carcinoma (22.5%) with a mean age of 65 years. There were 19 (12.5%) cases of MF. MF ranked as the third skin cancer in the order of frequency with a mean age of 44.6 years and male to female ratio of 3:1. Trends in MF with regard to age, gender of the patients, location histopathological and immunohistochemical features are summarized in Table 1, 2, 3 respectively .There was no case of MF recorded in less than 20 years of age at the time of diagnosis. The most common incidence was among males in the age group of 40-59 years 47.3%, followed by the age group of 20-39 years 36.8%. No statistical difference was observed in the mean age at diagnosis between male and female patients. The most common location was in the thighs 36.8%. Lesions were more common on the right side. The most common histological type was early or patch type 89.4%. The most reliable histological features for MF included hyperconvoluted epidermotrophic lymphocytes, dermal fibrosis, basal alignment of neoplastic lymphocytes and Pautrier's micro abscesses (Figure 2C). The atypical lymphocytes were positive for LCA and CD 3 (T cell markers Figure 1 D & E and Figure 2 E & F) and negative for CD 20 (B cell markers Figure 1 F and Figure 2 G) (Figure 1 and 2). They were also negative for CD 30 which was performed only in 10 cases depending on the availability of resources. CD 4 was performed in 5 cases as per availability and was positive in 4 (80%) of the cases. There was no family history of lymphoma or skin cancer in any of our patients neither did any of the patients have HIV or other forms of immune suppression.

Follow-up was available in 10 (52.6%) patients only. The mean duration of follow-up 24 months. At the last follow-up, 6 (31.5%) patients showed improvement, 2 (10.5%) patients showed deterioration, and 2 (10.5%) patients had no change in the disease status.

Discussion

While the term CTCL includes a number of rare disease entities, the most common subtypes are MF and SS, accounting for approximately 70–75% of all cases (9). Mycosis fungoides accounted for 72%of CTCL cases reported from 1973 to 2002,

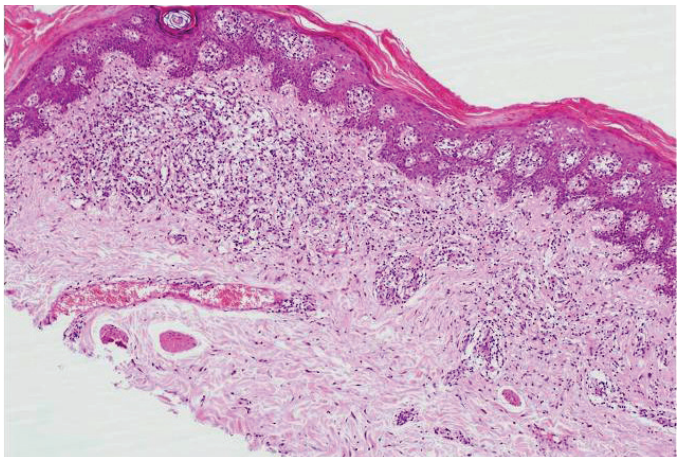

Figure 2A. Histologic section from early lesion showing hyperkeratosis, acanthosis, parakeratosis with superficial lymphoid infiltrate and dermal fibrosis

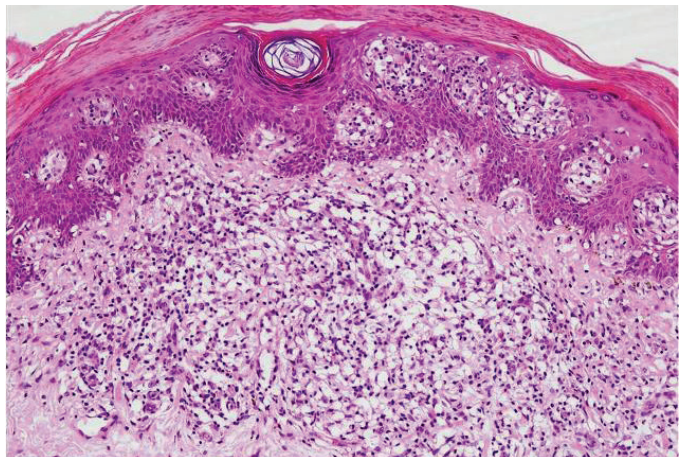

Figure 2B. Higher magnification showing epidermotropism of small to intermediate lymphocytes exhibiting halos mixed with dermal macrophages

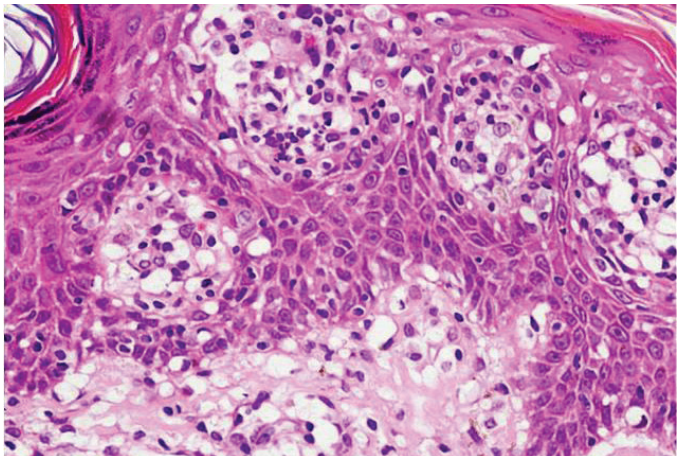

Figure 2C. Few Pautrier microabscesses are seen

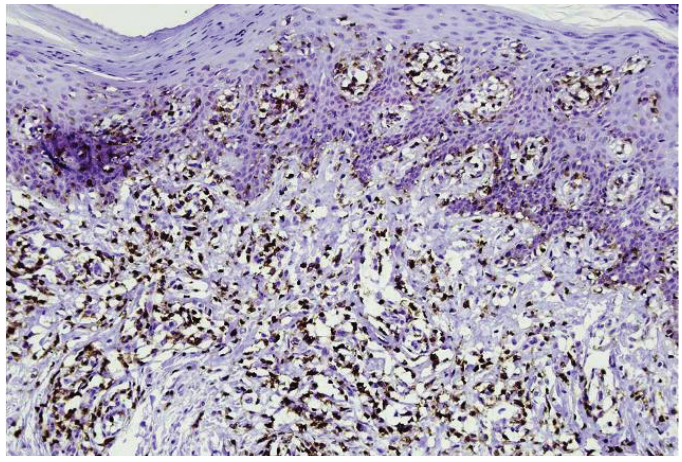

Figure 2D. LCA positivity in the atypical superficial dermal and epidermotrophic lymphocytic infiltrate

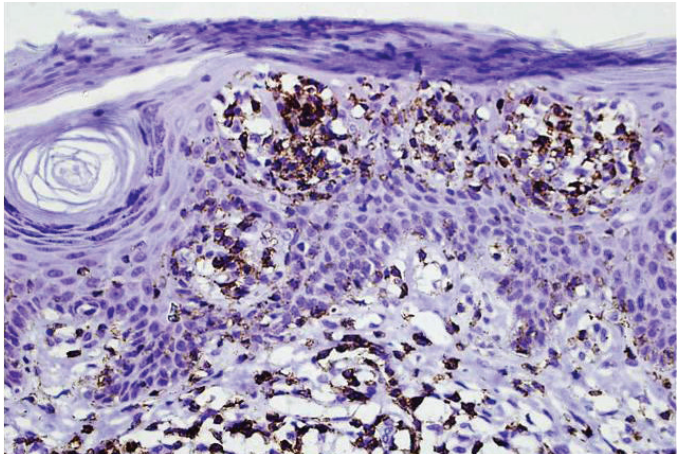

Figure 2E. CD 3 positivity in the atypical superficial dermal and epidermotrophic lymphocytic infiltrate.

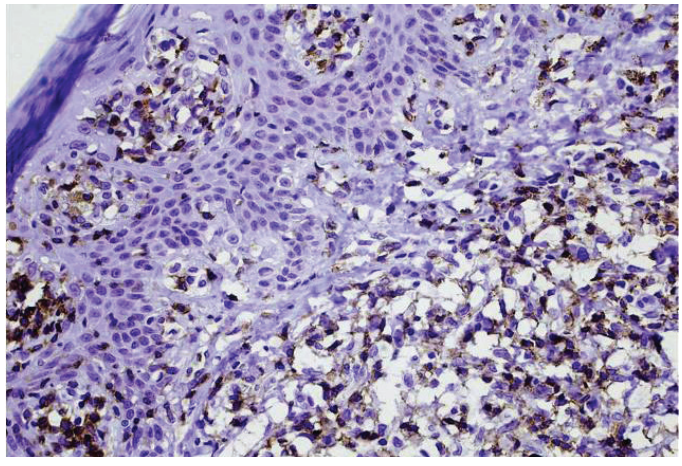

Figure 2F. CD 4 positivity in the atypical superficial dermal and epidermotrophic lymphocytic infiltrate.

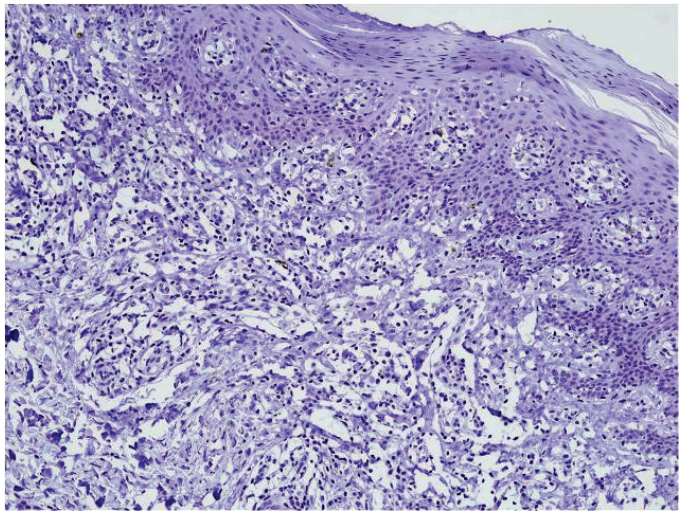

Figure 2G. Negative CD 20 in the atypical lymphocytes

whereas Sézary syndrome accounted for 2·5%2. Risk factors for development of MF include advanced age, black race, and male gender (2,10). The incidence of CTCL was roughly 50%greater in black people than in white people 2 especially in African Americans (7). Men are affected twice as often as are women, and incidence increases greatly with age (2,11).

In the present study MF ranked third in frequency of skin cancers among Saudis and showed male predominance. Male predominance was also reported by other studies from the region. Al magrabi reported 1%of MF from Al Baha12 exclusively in males. Recent studies from Riyadh reported 58 cases of MF with a male to female ratio of 1.9:113 and 43 patients with a male to female ratio of 2:113. Only one study of 5 patients of MF showed female predominance (15). The overall male predominance in the present study is consistent with other national (Table 4a 13-15) and international studies (2,6-10,16). The mean age in the present study of 44.6 years is consistent with the findings of a study from Riyadh (14) also reporting that MF tends to affect younger Saudis. Akhtar SS et al. (15) also reported mean age of 33 years for MF. Few cases of childhood MF have also been reported from Riyadh, Saudi Arabia (17). MF can be observed in children and early adults (18). A study targeting 193 cases of MF at a Dermatology Centre in Kuwait also reported MF among younger Arabs (19). A study from Iran also reported a younger age group (20). Tables 4b (16,19-22) presents the comparison with other international studies. These reports and the present study support the observation that younger age at diagnosis may represent a unique character of MF among Saudi and other Arab populations although they are discordant with the age reported in literature. The median age at diagnosis for MF is reported between 50–70 years of age (2,6-10,16).

This variation could be explained by a number of reasons such as; partly it may be due to the increasing awareness regarding different skin cancers among Saudi population bringing them to clinical attention early and at a younger age. It could also be partly attributed to the increased efficiency of detection following rapid improvements in health care over the past few decades in this region. Consistency in using proper case definitions and diagnostic criteria by clinicians and pathologists could also be partly responsible for this variation.

In early MF, the clinical findings can resemble other papulo-squamous disorders, such as eczema, contact dermatitis or psoriasis (8). MF lesions manifest as patches, plaques, tumours, or erythroderma and develop from the interactions of the neoplastic T cells with the cutaneous microenvironment (7). Mycosis fungoides typically presents in a "bathing suit" distribution including the hips, buttocks, thighs, lower abdomen, axilla, and breasts although any body surface may be affected (23). The most frequent locations of lesions in the thighs and legs in this study are in keeping with those mentioned in the literature. Patches may be asymptomatic or intensely pruritic. Repeated excoriation often results in secondary lichenification. Plaques may be annular, angulated, or serpiginous (23). Leonine facies results from malignant T-cell infiltration leading to extensive thickening and skin-fold accentuation (23).

Although in the present study 89.4% cases histologically corresponded to early/patch stage of MF the patients were subjected to repeat biopsies on many occasions. Skin biopsies at this stage may often be unhelpful and non-diagnostic (23). This phase can last for months or years before progressing to the classical plaque stage (23). In this early stage skin lesions may mimic eczema or papulo-squamous eruptions such as psoriasis, tinea corporis or secondary syphilis (23). Microscopically in the present study the most reliable criteria that emerged for differentiating negative cases from histologically confirmed MF included hyperconvoluted epidermotrophic lymphocytes, dermal fibrosis, basal alignment of neoplastic lymphocytes and Pautrier's micro abscesses (Figure 1 A, B and Figure 2 A, B and C). Hyperconvoluted epidermal, dermal lymphocytes and Pautrier's micro abscesses proved to be highly reliable with high specificity and sensitivity. Less sensitive and specific features were perivascular atypical lymphocytic infiltration and perinuclear halos. These histological features are in keeping with literature (11,24,25). The earliest histological changes seen in MF include a sparse, superficial patchy or perivascular lymphocytic infiltrate, slight epidermotropism, and occasional spongiosis (10,11,23-27). Mycosis fungoides cells display a predilection for keratinocytes, perhaps due to interaction with Langerhans' cells (23). Lymphocytic atypia, plasma cells, and eosinophils are rare (10,11,23-27). Within plaques, lymphoid cells in the upper dermis have hyperchromatic, convoluted nuclei and scant cytoplasm (10,11,23-27). Mononuclear cells are found within the papillary dermis as isolated "haloed cells" or in the epidermis as collections surrounded by a clear halo, Pautrier's microabscess, or microaggregation (10,11,23-27). There is psoriasiform epidermal hyperplasia with hyperkeratosis and focal parakeratosis (10,11,23-27). Epidermotropism, basal cell layer predilection, lymphocytic atypia, and Pautrier's microabscesses help distinguish MF from other dermatitis (10,11, 23-27).

With regard to immunophenotype, the hallmark of MF is expression of CD4, the marker of mature helper T-cells. A common MF immunophenotype is CD2 positive (pan T-cell marker), CD 3 positive (pan T-cell marker), CD4 positive (helper T-cell marker), CD5 positive (pan T-cell marker), CD45RO positive (memory T-cell marker), CLA positive (cutaneous lymphoid antigen), CD8 negative (cytotoxic T-cell marker), CD30 negative (activated T-cell marker) (8,26). The observations in the present study are consistent with the

literature as all the cases showed CD 3 expression with variable CD4 positivity. Most cases were negative for CD 20 and CD 30. Loss of pan T-cell marker expression, although uncommon, is highly specific for a diagnosis of MF (8,26). Further, low levels of CD7 expression (less than 10%) may help to distinguish early MF from benign mimics, and has a sensitivity of 40%and specificity of 80%to 100%(8,26). For a long time the neoplastic cell type in MF/SS was unknown, but with the ability to identify surface markers on the atypical T cells, it became apparent that MF and SS are malignancies of CD4+ CD45RO+ skin-homing T-cells (7). A recent study suggests that MF is a malignancy of skin resident effector memory T cells while SS is a malignancy of central memory T cells and as such arises from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors (28). Some studied suggest that presence of CD8+ lymphocytes in MF is associated with non aggressive biological behavior (29). Different patients affected by MF and SS show a specific chromosomal abnormality in the region between 1p22 and 1p36 (24,30). Familial links have been described for the incidence of multiple MF cases within single families or the occurrence of other hematologic malignancies in families of individuals diagnosed with MF24. An infectious etiology for MF has been suggested but no relation has been confirmed (2,24). Human T-lymphotropic virus type I (HTLV-I) has been reported in the peripheral blood or cutaneous lesions of some patients with MF or Sezary syndrome but an equal number of studies have evidence against a role of HTLV-I (24). Some groups have found serologic evidence of the Epstein-Barr virus in MF patients, suggesting a possible role in the pathogenesis, although it may be simply a bystander virus (7,24). The cytokines interleukin-7 (IL-7) and IL-15 have been suggested to play a role in the development of MF (7,24). These two cytokines, which are also produced in the skin, may be responsible for the epidermotropism of this disease (7,24).

At the molecular level assays for clonalit with respect to molecular assays for clonality in MF polymerase chain reaction (PCR)-based techniques identify a dominant clonal T-cell receptor (TCR)-γ rearrangement in 63%to 90%of skin biopsies that show definite histologic evidence of MF (11). Southern blot analysis and PCR-based methods are able to detect clonal rearrangements of the T-cell receptor (TCR) in formalin-fixed, paraffin-embedded biopsy specimens (26). Furthermore, PCR identifies a TCR gene rearrangement in 50%to 80%of histologically borderline biopsies obtained from patients who subsequently develop classic MF (11).

All patients in the current study had skin confined lesions; none had enlarged lymph nodes at last follow up. MF is typically an indolent malignancy and often presents with a premycotic phase. Multiple skin biopsies over many years are needed typically for a diagnosis (31). Survival correlates with the stage of initial presentation (31). Patients presenting with skin-restricted patches and plaques that affect <10%of the body surface area, have an excellent prognosis, and in analysis of long-term survival, patients with minimal skin disease have survival comparable to the normal age matched cohort (31,32).

This study has certain limitations and the results should be interpreted keeping them in mind. Although the study was carried out using validated hospital database, the author cannot assume that information bias was absent (mainly generated in the patient profile and result entry process). Actions were taken to address this issue, such as exhaustive personal verification of clinical and demographic data. Another limitation was the small number of cases which further limits the application of these results to the Saudi population at large.

In conclusion, MF is a rare tumor and ranked third in frequency of skin cancers among Saudi patients showing predilection for younger males which highlights the ethnic and/or regional variation in the clinico-epidemiological characteristics of MF.

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Kaynaklar

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