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Original Article

Mycosis fungoides in Iraqi population; changing in frequency, demographic and clinical subtypes

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Abstract

Background Mycosis fungoides (MF) is a slow-progressing primary cutaneous T-cell lymphoma. where we see the classical picture of the disease without much attention to other clinical variants of the disease. While there is a paucity of literature on this condition in Iraqi population.

Objective To record and evaluate the different socio-demographic factors and clinical patterns of mycosis fungoides and their variants in Iraqi patients.

Methods The current study comprised a total of 108 participants with MF. All patients had a complete medical history and were evaluated clinically. Histopathology was performed on incisional biopsies. Only 20 patients were studied using immunohistochemistry. Laboratory tests including blood cell-count, blood levels of creatinine, urea, liver enzymes, and lactate dehydrogenase (LDH). Main outcome measures are age, gender, duration of disease, clinical subtypes, lesions distribution and staging.

Results Fifty eight (53.7% patients had patch stage, 34 (31.5%) in the plaque stage, 8 (7.4%) in the tumor stage and 8 (7.4%) patients presented with erythroderma. In regards to clinical variants: poikiloderma was seen in 44 (40.7%) patients, lichenoid variant was seen in 12 (11.11%) patients, hypopigmented variant in 5 (4.6%) patients, follicular MF in only one patient and granulomatous in one patient. While the ordinary classical picture observed in 45 (41.66%) patients. The most common stage at diagnosis was IA (42 patients), followed by IB (32patients), IIA (18 patients), IIB (8 patients) and III (8 patients) . Palpable lymph nodes were detected in 18 (16.66 %) patients while visceral involvement was not detected in any patient.

Conclusion Clinical pattern of MF at time of presentation has changed, mostly toward unusual variants of MF commonly poikilodermoid subtype. The rate of MF is higher in males than females. There seems to be increase in frequency of this disease which go parallel with increase of other skin tumors.The reason behind this rise could be well attributed to situation of Iraq as for decades, it had been a stage for many wars in which almost all kinds of weapons have been used, where the depleted uranium is the most important incriminated factor.

Key words
Mycosis fungoides, depleted uranium, mycosis fungoides variants.

Introduction

The most frequent kind of primary cutaneous T-cell lymphoma (CTCL) is mycosis fungoides (MF), which is a cancer of mature, skin-homing T cells. MF is characterized by erythematous patches and plaques, and it acts like a low-grade lymphoma with a slow progression.[1] MF generally affects elderly people, with a male to

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female ratio of 1.6–2:1 at the time of diagnosis. Since 1995, the incidence rate has remained consistent at roughly 5.6 per million people. It can also happen in children and teenagers on a very uncommon basis.[2] The normal presentation of this disease consists of three stages: a premycotic stage with non-specific erythematous and scaling lesions; a mycotic stage with non-specific erythematous and scaling lesions; and a mycotic stage with non-specific erythematous and scaling lesions. The infiltration of pre-existing erythematous-squamous plaques, as well as the appearance of new infiltrated plaques and nodules, characterize the second stage. Although early tumor types are rare, a third stage is identified by the emergence of tumors of varied sizes with an erythematous light-brown color. Both the clinicopathological and immunophenotypic manifestations of MF are diverse. Poikilodermatous mycosis fungoides (PMF), also known as poikiloderma vasculare atrophicans (PVA), is a rare clinical variation of early-stage MF characterized by mottled hypopigmentation and hyperpigmentation, atrophy, and significant telangiectasia (poikiloderma). Lesions prefer the trunk (particularly the breasts) and buttocks, however they can be found anywhere. Atrophic epidermis, loss of rete ridges, band-like lymphocyte infiltrate, epidermotropism, dilated capillaries, necrotic keratinocytes, pigment incontinence, and a thicker papillary dermis are all histological findings in PMF.[3] In comparison to the traditional type, the hypochromic variation has exhibited its own unique epidemiological characteristics. This variant is obvious at the outset in young patients and exhibits no male/female preference, in addition to being uncommon in white patients in relation to age. The majority of the time, patients responded quickly to treatment. There are no characteristic mycosis fungoides lesions in the pure hypopigmentary form.[4] When compared to other clinical forms of MF, PMF had a lower risk of disease progression and improved survival, just like hypopigmented MF.[3] Folliculotropic mycosis fungoides (FMF) is a well-known and unique form of mycosis fungoides. FMF appears as acneiform lesions with comedo-like plugs and epidermal cysts, follicular papules, follicular keratoses, erythematous patches and plaques, and hair loss in affected areas. The face, neck, and upper body are particularly vulnerable. FMF is defined histopathologically by extensive lymphocytic infiltrates around and penetrating the hair follicles, with interfollicular skin being spared. Cystic dilatation, clogging, and mucus deposition are common in follicles.[5]

The rarest form of MF is hyperpigmented lichenoid MF, with just nine cases reported to date.[6] Individuals with a dark complexion and a younger age, usually less than 35 years old, are more likely to be affected than patients with classic MF. Without evidence of poikilodermatous alterations, it appears as hyperpigmented patches and plaques. In addition to epidermotropism and dermal infiltration of lymphocytes, the histology is characterized by interface changes with melanophages on hematoxylin-eosin staining, as well as epidermotropism and dermal infiltration of lymphocytes, and immunohistochemically by a predominantly CD8+ cell population.[6]

Patients and methods

This is an observational case series clinical study that took place from 2006 to 2019 at the Department of Dermatology at Baghdad Teaching Hospital, Medical City, Baghdad, Iraq. A total of 108 individuals with MF were included in this study, with the majority of them being visited by just one clinician (Sharquie KE). Each patient had a thorough history and physical examination that included all socio-demographic elements of the condition. All patients had incisional biopsies taken from the

most representative skin lesions at various places. Due to the terrible circumstances of the country, we were only able to undertake immunohistochemistry studies on 20 patients because the test was not available in our institution. CD3, CD4, CD8, CD20, and CD30 lymphocyte markers were used as primary antibodies. All patients underwent laboratory tests, including a blood cell count, creatinine, urea, liver enzymes, and lactate dehydrogenase levels (LDH). The histological criteria given by Smoller *et al*.[7] were used to make the diagnosis of MF, which included the following:

1) Lymphocyte atypia is characterized by nuclear enlargement, hyperchromasia, and irregular nuclear outlines or cerebriform morphologic characteristics.
2) Lymphocytic epitheliotropism, characterized by the formation of Pautrier microabscesses.
3) Morphologically abnormal lymphocytes are aligned on the epidermal side of the dermo-epidermal junction.
4) Papillary dermal expansion with coarsened collagen fibers and dense infiltration of morphologically abnormal lymphocytes.

A definitive diagnosis of MF required the presence of at least three of the four morphologic criteria for MF.

All patients were staged according to TNMB WHO classification updated in 2016. Main outcome measures were: age, gender, duration of disease, clinical subtypes, lesions distribution and staging.

After data collection; statistical analysis was performed by SPSS (Statistical Package for the Social Scienc) soft ware version 22.

Results

Over the course of 13 years, a total of 108 MF patients were seen. There were 81 males and 27 females, for a male to female ratio of 3:1. Fitzpatrick skin types 3 and 4 encompass all patients. Their ages ranged from ten to seventy years old, with a mean SD of 45.53±14.96. In 56 (51.85%) of patients, the most prevalent age group afflicted was 40-59 years old **(Table 1)**. The sickness lasted anywhere from 1 to 36 months, with a mean SD of 15.95±9.34 months. In this study, 6 (5.6%) cases of childhood MF were identified, with clinical symptoms ranging from a single patch in two patients to hypopigmented patches in two patients to poikodermatous patches in two children, all of whom had dark skin. In varied quantities, all bodily sites were implicated. The most common region implicated was the trunk, whereas the head and neck were the least involved.

58 (53.7%) patients had patch stage lesions, 34 (31.5%) had plaque stage lesions, 8 (7.4%) had tumor stage lesions, and 8 (7.4%) had erythroderma.

In regards to clinical variants: poikiloderma was seen in 44 (40.7%) patients **(Figure 1)**, lichenoid variant was seen in 12 (11.11%) patients **(Figure 2)**, hypopigmented variant in 5 (4.6%) patients, granulomatous MF in one patient and follicular MF in only one patient **(Figure 3)**. While the ordinary classical picture observed in 45 (41.66%) patients.

The MF staging was done according to the TNMB staging system. IA (42 patients) was the

Table 1 Shows the age of patients distribution.

Age groups	*N*	*%age*
10 - 19 years	6	5.6%
20 - 29 years	5	4.6%
30 - 39 years	18	16.7%
40 - 49 years	26	24.%
50 - 59 years	30	27.8%
60 - 69 years	18	16.7%
>=70 years	5	4.6%
Total	108	100%

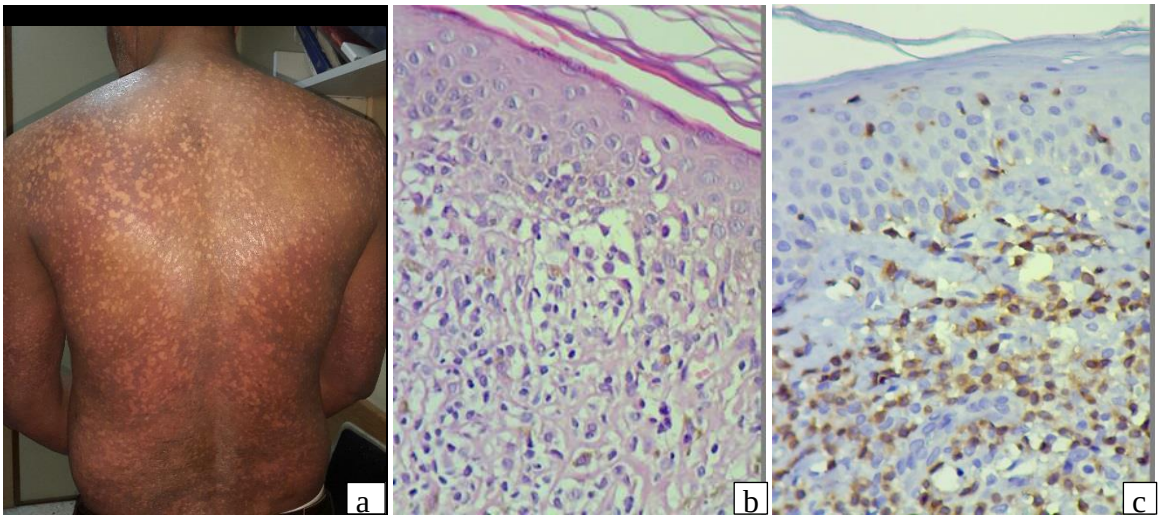

Figure 1 (a) middle age man with poikilodermatous mycosis fungoides affecting the trunk. **(b) H & E stain ×400** Microscopic view showing epidermal atrophy with superficial perivascular infiltrate in dermis with epidermotropism. Pautrier microabscesses destroying the dermal-epidermal junction. **(c)** ×400 positive CD4 staining.

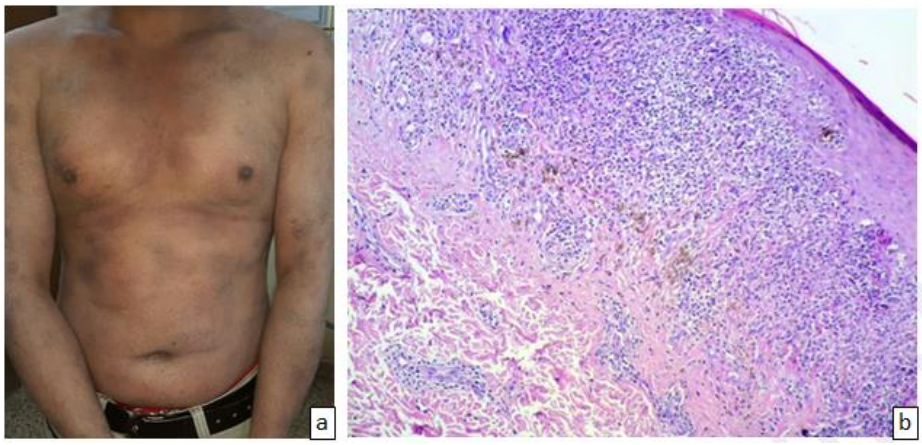

Figure 2 (a) young man with lichenoid hyperpigmented mycosis fungoides affecting the trunk and extremities **(b)** H & E stain ×100 Microscopic view showing lichenoid infiltrate in dermis with atypical lymphocytes and epidermotropism destroying the dermal-epidermal junction. Melanin incontinence is especially noticed.

most prevalent stage at diagnosis, followed by IB (32 individuals), IIA (18 patients), IIB (8 patients), and III (8 patients) **(Table 2)**.

Table 3 Staging according to TNMB system of MF.

Staging	*Frequency*	*Percent*
IA	42	38.9%
IB	32	29.6%
IIA	18	16.7%
IIB	8	7.4%
III	8	7.4%
IV	0	0%
Total	108	100%

Palpable lymph nodes were detected in 18 (16.66 %) patients while visceral involvement was not detected in any patient.

On immunohistochemical studies, 19 patients were positive for CD3 , CD 4, and negative for CD 20 and CD8 Figure 4, only one patient was double negative for CD4 and CD8 and positive for CD3.

Discussion

Mycosis fungoides (MF) is the most common

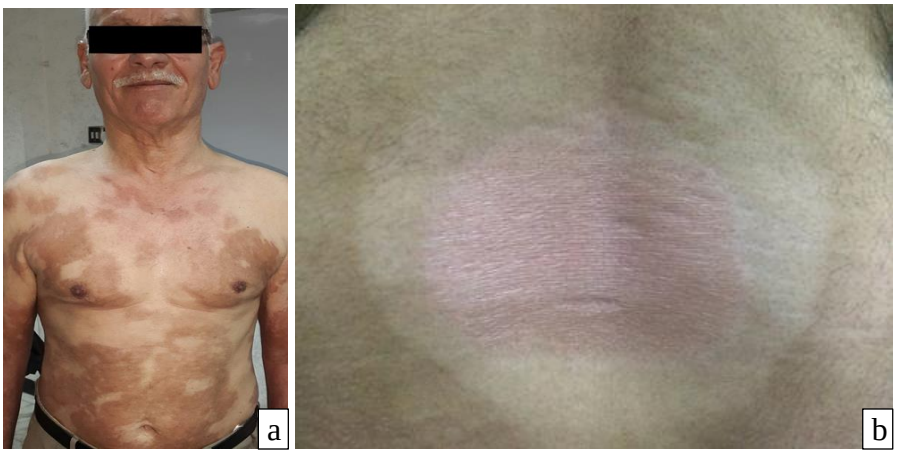

Figure 3 (a) an old man with hypopigmented mycosis fungoides affecting the trunk and extremities **(b)** another patient with follicular MF affecting the lower back with marked hair loss.

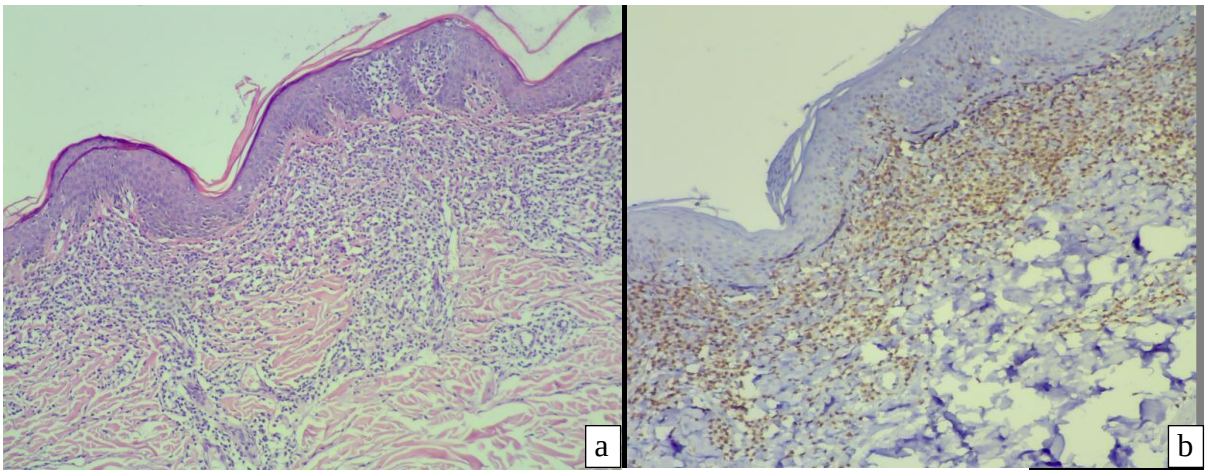

Figure 4 (a) H & E stain ×100 microscopic view showing epidermis with pautrier microabscess **(b)** ×100 Immunohistochemical staining for the same patient was positive for CD4.

type of primary cutaneous T-cell lymphoma (CTCL), with an estimated incidence of 0.5 per 100,000 people per year in the Western World. However, we do not know the exact prevalence of MF in Iraq due to a lack of local statistics.

Prior to 1980, MF was extremely rare in Iraq, but its prevalence has been steadily increasing since then, as evidenced by two previous Iraqi studies.[8,9] This work reveals additional evidence of this upsurge in MF case in Iraq, as we records 108 patients with MF seen in only one Center within thirteen years. This comes in concordance with the rise in other skin tumors like Kaposi sarcoma, squamous cell carcinoma and Paget's disease.[10-12] The cause of this upsurge is not clear but it could be related to exposure to chemical weapons and depleted uranium during the consequent wars that Iraq had faced since 1990.

The age of onset at the present study was 45.53 years which is comparable to the previous two Iraqi studies (42.6 and 47.5 years respectively).[8,9]

Although MF is typically present in older ages, it often represents the most diagnosed Primary cutaneous lymphoma in childhood.[13] In this work, we have reported 6 cases of childhood

MF, their clinical picture varies from single patch in 2 patients, hypopigmented patches in 2 patients and poikodermatous patches in 2 patients where all dark-skinned type.

There is a male predilection with male to female ratio 3:1 which is consistent with the previous studies.[8,9]

The present study showed a change in clinical behavior of MF, shifting it from the classical picture to more unusual variants that were unfamiliar to most physicians. Poikiloderma was seen in 44 (40.7%) patients, lichenoid variant was seen in 12 (11.11%) patients, hypopigmented variant in 5 (4.6%) patients granulomatous MF in one patient and follicular MF in one patient. Poikilodermatous mycosis fungoides (PMF) in particular appears to be more dominant picture observed in the present work, although it is a rare clinical variant of early-stage MF around the world.[14]

In Iraq, vitiligo frequently manifests as stage I and stage II depigmentation, with histology that has been compared to early MF and even the formation of pautrier microabscess.[15] The hypopigmented variant was seen in adult patients, but it was more commonly reported in children in places like Saudi Arabia (41.1 percent) and Kuwait (64%); this high frequency of this variant could be due to misdiagnosis with stage I vitiligo rather than true hypopigmented MF[16,17] which was probably stage one depigmentation of vitiligo rather than mycosis fungoides as all of them end with very good prognosis.

Conclusion

The frequency of MF seems to be increasing in concordance with the rise in other types of skin tumors where depleted uranium was frequently accused. The rate of MF is higher in males than females. The present work also revealed that the clinical pattern of MF at time of presentation has changed, mostly toward unusual variants of MF like poikilodermoid type.

References

1. van Doorn, R., van Kester, M. S., Dijkman, R., Vermeer, M. H., Mulder, A. A., Szuhai, K., Knijnenburg, J., Boer, J. M., Willemze, R., & Tensen, C. P. (2009). Oncogenomic analysis of mycosis fungoides reveals major differences with Sézary syndrome. *Blood*. **113(1)**:127-136.
2. Denis D, Beneton N, Laribi K, Maillard H. Management of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL): focus on chlormethine gel. *Cancer Manag Res*. 2019;**11**:2241-51.
3. Gulin SJ , Čeović R, Ilić I , Bradamante M , Mokos ZB , Kostović K. Poikilodermatous Mycosis Fungoides – Rare Entity, Different Treatment Modalities. *Acta Dermatovenerol Croat*. 2018;**26(1)**:48-52.
4. Duquia Rodrigo Pereira, Souza Paulo Ricardo Martins, Gervini Roberto Lopes, Schwartz Joel, Prochnau Auro, Almeida Jr Hiram Larangeira de. Hypopigmented mycosis fungoides with 20 years evolution. *An Bras Dermatol*. 2005;**80(2)**:189-91.
5. Yonan YA, Cumsky HJL, Costello CM, *et al*. Syringotropic and folliculotropic mycosis fungoides with mycosis fungoides-associated vasculopathic ulcers. *JAAD Case Rep*. 2019;**5(3)**:231–3.
6. Lu YY, Wu CH, Lu CC, Hong CH. Hyperpigmentation as a peculiar presentation of mycosis fungoides. *An Bras Dermatol*. 2017;**92**:92-4.
7. Smoller, B.R., Bishop, K., Glusac, E., Kim, Y.H. and Hendrickson, M.Reassessment of Histologic Parameters in the Diagnosis of Mycosis Fungoides. *Am J Surg Pathol*.1995;**19**:1423-30.
8. Ali, A.N. Mycosis Fungoides in Iraqi Patients a Clinical and Histopathological Study. A Thesis Submitted to Iraqi Board for Medical Specializations, Dermatology and Venereology 1999.
9. Al-Hamamy H, Sharquie KE, Naomi A, Abdulwahhab W. Mycosis Fungoides in Iraqi Patients-Clinical, Histopathological and Immunohistochemical Study. *J Cosmet Dermatol Sci Appl*. 2015;**5(2)**:116-24.

10. Al-Waiz M1, Sharquie KE, and Al-Hamdani GA. An upsurge of new cases of Kaposi's sarcoma in Iraqi patients. *Saudi Med J*. 2003;**24(2)**:224-5.
11. Sharquie K.E., and Al-Janabi W.K. Squamous Cell Carcinoma of Lower Lip: Topical Podophyllin is an Alternative Therapy for Early Cases. *Am J Dermatol Venereol*. 2019;**8(4)**:61-5.
12. Sharquie K.E., and Al-Janabi W.K. Paget's Disease: Striking Clinical Findings and With New Palliative Topical Therapy Using 25% Podophyllin. *Cancer Sci Res*. 2019;**2(2)**:1–6.
13. Gameiro A., Gouveia M., Tellechea Ó., Moreno A. Childhood hypopigmented mycosis fungoides: a commonly delayed diagnosis. *BMJ Case Rep*. 2014;**2014**:bcr2014208306.
14. Van Doorn R, Van Haselen CW, van Voorst Vader PC, *et al*. Mycosis Fungoides: Disease Evolution and Prognosis of 309 Dutch Patients. *Arch Dermatol*. 2000;**136(4)**:504–10. doi:10.1001/archderm.136.4.504.
15. Sharquie, K.E., Mehenna, S.H., Naji, A.A. and Al-Azzawi, H. Inflammatory Changes in Vitiligo: Stage I and II Depigmentation. *Am J Dermatopath*.2004;**26**:108-12.
16. AlGhamdi, K.M., Arafah, M.M., Al-Mubarak, L.A., Khachemoune, A. and Al-Saif, F.M. Profile of Mycosis Fungoides in 43 Saudi Patients. *Ann Saudi Med*. 2012;**32**: 283-7.
17. Nanda, A., AlSaleh, Q.A., Al-Ajmi, H., Al-Sabah, H., Elkashlan, M., Al-Shemmari, S. and Demierre, M.-F. Mycosis Fungoides in Arab Children and Adolescents: A Report of 36 Patients from Kuwait. *Pediatr Dermatol*. 2010;**27**:607-13.