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# Mycosis Fungoides in Iraqi Patients—Clinical, Histopathological and Immunohistochemical Study

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## Abstract

**Background: Mycosis fungoides (MF) is not an uncommon T-cell lymphoma in Iraqi population which is increasing over years. There are many diagnostic techniques to confirm the diagnosis including histopathological and immunohistochemical tests. Objectives: To evaluate all cases of MF including clinical, histopathological and immunohistochemical tests with CD markers. Patients and Methods: This clinical, histopathological, immunohistochemical outpatient based study took place in the Department of Dermatology, Baghdad Teaching Hospital, Medical City, Baghdad, Iraq during the period from May 2012-September 2013. Twenty five patients with MF were included in the present work. History was obtained from each patient regarding all socio-demographic aspects related to the disease. Also, clinical evaluation was carried out for all patients. Incisional biopsies for ordinary histopathology and immunohistochemical tests were done. Then staging was carried out depending on TNMB classification for all patients. Results: All cases of MF were confirmed after clinical evaluation, histopathology and immunohistochemical examination. Male to female ratio was 1.5:1. The mean age of onset at presentation was 47.45 ± 16.9 years. Itching was found in 84% of cases. The patch stage was seen in 36% patients. The hypopigmentaed MF was presented in 12% cases. The lower extremities were seen in 80%. Lymph node involvement as a manifestation of the disease was seen in 44% cases. The histopathological features of MF went parallel with the clinical stage of disease. Immunohistochemical study aids in the diagnosis of**

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**patch and erythrodermic stages. The most patients presented with stage IB (36%). Conclusion: MF seems to be not uncommon problem in Iraqi population and is increasing over years. The disease was diagnosed early commonly with patch stage (stage $I_B$) while hypopigmented MF was not a common variant when compared with neighboring countries.**

## Keywords

**Mycosis Fungoides, T-Cell Lymphoma, Immunohistochemical Examination, TNMB Classification**

## 1. Introduction

Mycosis fungoides (MF) is the most common form of cutaneous T cell lymphoma (CTCL) and accounts for almost 50% of all primary cutaneous lymphomas [1]-[3]. MF has an indolent clinical course with slow progression over years or decades, from patches to more infiltrated plaques and, eventually tumors [4] [5]. The incidence of MF has been reported in USA to be 0.4 per 100,000 per year [6]. Its pathogenesis involves interplay of genetic, environmental and immunologic factors [5] [6].

The clinical manifestations are variable and MF is considered in the differential diagnosis of many skin diseases [7]. Histopathological study is essential in the diagnosis, but the results are not always conclusive [8] [9]. Immunohistochemical techniques have been used more frequently in recent years to establish the diagnosis in recent years [10].

In Iraq, MF was very rare before 1980 and since then cases are increasing and this is well established by Iraqi study carried out between March 1998 and August 1999 where 20 cases were diagnosed within this period [11]. This increase was attributed to depleted uranium that has used by American army. In this study the age of onset was averaged between 23 - 64 years with a mean of 42.65 ± 11.65 years. The mean duration of the disease was 7.9 ± 5.14 years. Males were affected twice as females in a ratio of 2:1. The most common presentation was stage IB (75%) and no hypopigmented MF was included [11]. Accordingly the aim of the present work is to report this increasing frequency of this disease and to characterize the different clinical pictures and staging of the disease.

## 2. Patients and Methods

This is a clinical, histopathological, immunohistochemical outpatient based study. It was carried out at the Department of Dermatology at Baghdad Teaching Hospital, Medical City, Baghdad, Iraq during the period from March 2012 to September 2013. A total of 25 patients consulted the department at the specified period and were diagnosed as having MF. All these patients were included in the study.

Full history and physical examination were performed for each patient regarding all socio-demographic aspects related to the disease. Skin biopsy and immunohistochemical study were carried out in all patients. Incisional biopsy was done for all patients from the most representative skin lesions at variable sites. Lymph node biopsies were done for four patients who presented with palpable lymph glands.

The diagnosis of MF was based on the histological criteria proposed by Smoller *et al.* [9], these include the following:

1) Lymphocyte atypia defined by nuclear enlargement, hyperchromasia, and irregular nuclear contours or cerebriform morphologic features.

2) Epitheliotropism of lymphocytes, including formation of Pautrier microabscesses.

3) Alignment of morphologically atypical lymphocytes along the epidermal side of the dermo-epidermal junction.

4) Expansion of the papillary dermis with coarsened collagen fibers that contain a dense infiltrate of morphologically atypical lymphocytes.

A definitive diagnosis of MF required at least 3 of the 4 morphologic criteria for MF to be present [9].

Formalin-fixed, paraffin-embedded tissue sections from each biopsy specimen were deparaffinized in xylene and absolute ethanol and then rehydrated by successive immersions in 95% ethanol, 70% ethanol, and distilled water. All immunoperoxidase staining was performed on DAKO instrument (DAKO, Glostrup, Denmark), using

an automated immunostainer (DAKO) using the avidin-biotin-peroxidase complex. Primary antibodies to lymphocyte markers CD3, CD4, CD8, CD20, and CD30 were applied.

Quantification of T-cell subsets was performed at high power fields of CD3 stained slides for each case. CD4 and CD8 positive stained cells were counted and percentages of results were expressed separately for the epidermal and dermal inflammatory compartments, on a 10% scale (e.g. 0%, 10% and 20%). Final CD4/CD8 ratio was determined by dividing the CD4 percentages on the CD8 percentages.

CD4, CD8 positive cells in the epidermis were counted from the basement membrane up to the stratum corneum across were on at least 4 randomly selected high power fields (×100). Cells in the dermis were counted from the basement membrane down to subcutaneous tissue on at least 4 randomly selected high power fields (×100). Dermal and epidermal CD4: CD8 for patients in patch-stage MF and erythrodermic MF. This ratio helps in confirming the diagnosis of MF in suspicious cases.

After full assessment, staging of the disease was done according to TNMB staging classification. Formal consent was taken from each patient after full explanation about nature of present study and the goal of the present work. Also ethical approval was performed by the Scientific Council of Dermatology and Venereology–Arab Board for Medical Specializations.

Color photographs for each patient were taken using Sony-digital, high sensitivity, 16.1 megapixel camera in the same place with fixed illumination and distance.

Data were statistically described in terms of range, mean, standard deviation (±SD), mode and frequencies (number of cases) and relative frequencies (percentages). All statistical calculations were done using computer statistical programs SPSS ver.20 (Statistical Package for the Social Science; SPSS Inc. Chicago, IL, USA).

## 3. Results

***Demographic Criteria*:** A total of 25 patients with MF were diagnosed as MF during the study period. Fifteen of them were males and ten were females with male to female ratio 1.5:1.

Their ages at presentation ranged between 18 - 80 years with a mean ± SD of 49.92 ± 16.94 years. **Table 1** shows the age at presentation of the patients by decades. The most common decade was the 7$^{th}$ decade (24%). It was interesting to note that two (8%) patients were in their second decade of life. The duration of the disease before diagnosis ranged from 1 - 60 months with a mean ± SD of 23.08 ± 20.34 months.

Pruritus was complaint of by 21 (84%) patients. Pruritus was mild in 10 patients, moderate in 9 patients and a severe in 2 patients.

Family history of MF was positive in one (4%) patient. This patient was a 45 years old male presented with tumor stage MF distributed all over the body (12 lesions) with palpable axillary and inguinal lymph nodes which proved by LN biopsy to be involved by the disease. This patient died after 6 months of diagnosis due to visceral involvement. His brother suffered from the same condition before 10 years and died because of the disease.

All body sites were involved in different proportions. However, the lower extremities were the most common site of involvement with the total number of lesions equals 83 lesions and the head and neck were the least with a total number of 22 lesions (**Table 2**).

**Table 1.** Showing the age of patients at presentation.

| Age groups | Number of patients | Percent of total |
|---|---|---|
| 10 - 19 years | 2 | 8.0 |
| 20 - 29 years | 1 | 4.0 |
| 30 - 39 years | 4 | 16.0 |
| 40 - 49 years | 4 | 16.0 |
| 50 - 59 years | 4 | 16.0 |
| 60 - 69 years | 6 | 24.0 |
| >=70 years | 4 | 16.0 |
| Total | 25 | 100.0 |

Regarding the morphology of the lesions: 11 (44%) patients had patch stage, 3 (12%) in the plaque stage, 9 (36%) in the tumor stage and 2 patients presented with erythroderma (**Figure 1**).

Palpable lymph nodes were detected in 11 (44%) patients. Palpable axillary lymph glands were detected in 10 (40%) patients, cervical lymph glands were detected in one (4%) patient and inguinal lymph glands were palpable in 7 (28%) patients at the time of presentation. Their sizes were ranged between 1 - 2.5 cm in diameter they were rubbery, mobile and not tender. Lymph nodes biopsies were performed for 4 patients who showed involvement of lymph glands by neoplastic lymphoid cells.

The staging of MF was carried out according to TNMB staging system. The most common stage at diagnosis was IB (9 patients), followed by IVB (5 patients). While stage IIB was diagnosed in 3 patients and 2 patients

**Table 2.** Showing the distribution of lesions according to the site.

| Site of involvement | Involvement | | Total number of lesions |
|---|---|---|---|
| | Number of patients | 56.5% | |
| Head and neck | 8 | 32% | 22 |
| Chest | 18 | 72% | 48 |
| Abdomen | 19 | 76% | 58 |
| Back | 11 | 44% | 32 |
| Upper extremities | 14 | 56% | 58 |
| Lower extremities | 20 | 80% | 83 |
| Gluteal area | 9 | 36% | 18 |

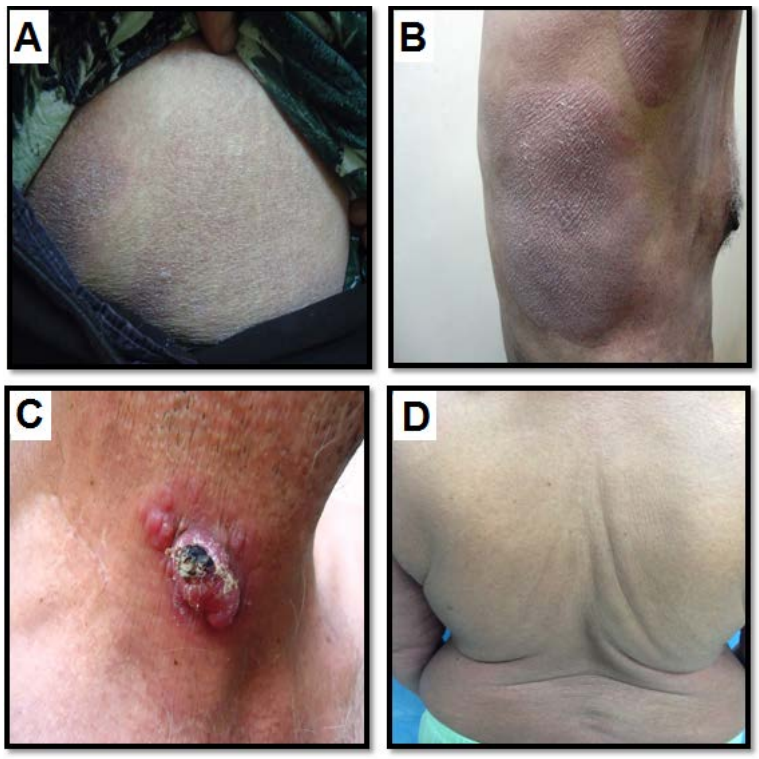


**Figure 1.** Clinical types of MF. (A) Patch stage MF: ill-defined brownish to violaceous scaly patches; (B) plaque stage MF: multiple well defined brownish scaly plaques; (C) tumor stage MF: mushroom-like masses on the neck; (D) Erythrodermic MF: the skin is diffusely scaly red.

were diagnosed in the stage IA, IIA, IVA (**Table 3**). Visceral involvement was detected in 3 (12%) patients.

***Histopathology*:** The most common features in histopathology were as follows (**Figure 2** and **Figure 3**):

- Large atypical lymphocytes (25 cases, 100%).
- Reaction pattern of lymphocytes in papillary dermis (24 cases, 96% ).
- Epidermotropism of lymphocytes (21 cases, 84%).
- Band like distribution of atypical lymphocytes (18 cases, 72%).
- Papillary dermal fibrosis (12 cases, 48%).

Less common features include multinucleated giant cells (one case), neutrophils (two cases) and diffuse in volvement of dermis and panniculus (two cases).

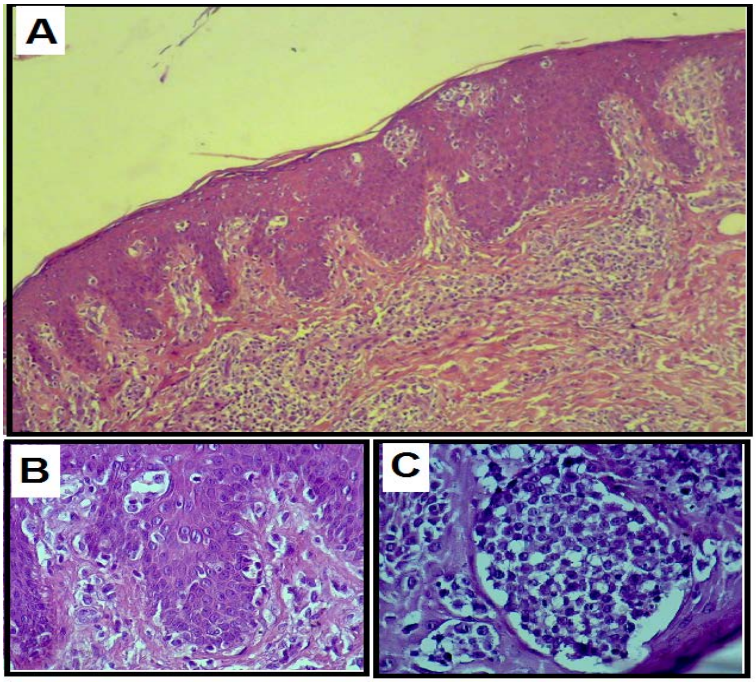


**Figure 2.** Hematoxylin and eosin (H & E) stained section of patch stage MF. (A) Psoriasiform epidermis and expansion of the papillary dermis with coarsened collagen fibers that contain a dense infiltrate of morphologically atypical lymphocytes (Magnification ×10); (B) permeation of epidermis by singly scattered atypical and hyperchromasia lymphocytes (Magnification ×40); (C) large Pautrier microabscess formed by clustering of atypical looked lymphocytes surrounded by clear space within epidermis (magnification ×40).

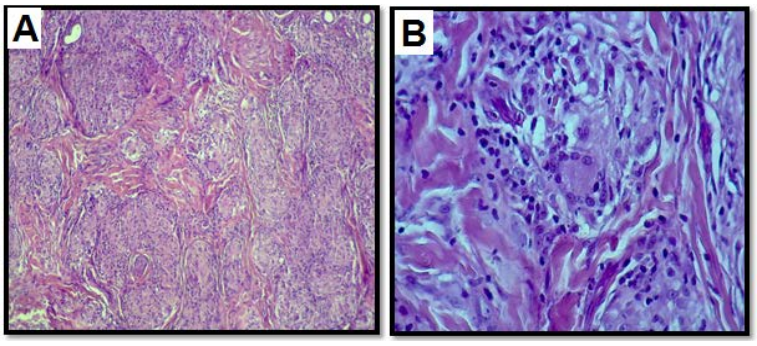


**Figure 3.** Granulomatous mycosis fungoides (sarcoid like) showing dense nodular lymphocytic infiltrates throughout the entire dermis. Multinucleated histiocytic giant cells were present. (Hematoxylin-eosin, original magnification ×10 (A); ×40 (B)).

***Immunohistochemistry***: CD3+ was detected in all patients. CD4+ T cells were detected in 21 patients and CD8+ in 19 patients. CD20 was negative in all patients. CD30 was positive in one patient. **Table 4** showed the range and average of CD4/CD8 ratio in patients with patch stage and erythrodermic stage of MF. CD30 positive T cells were detected in one patient with tumor stage. He was diagnosed to be large anaplastic T cell lymphoma (**Figure 4**).

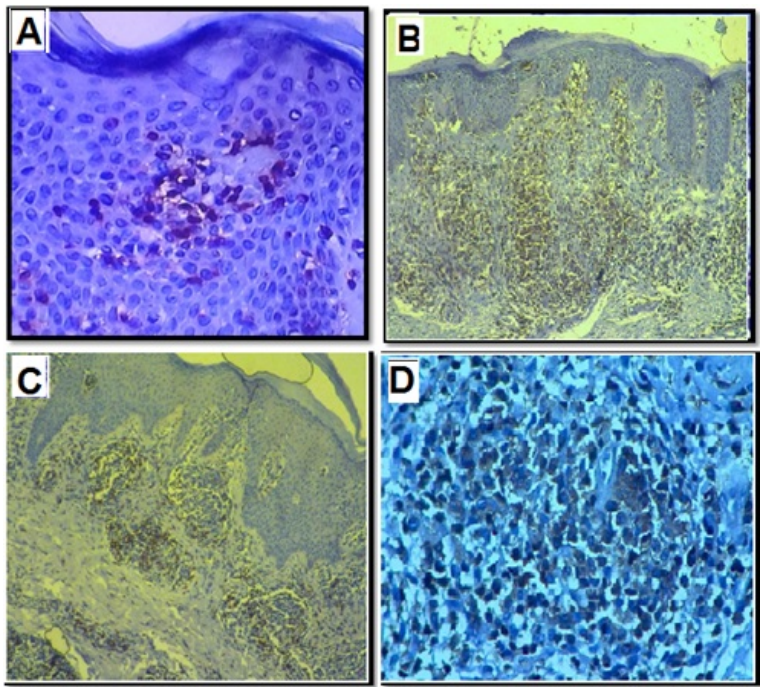


**Figure 4.** Hematoxylin and eosin (H & E), CD markers staining of skin specimens from patients with mycosis fungoides. H&E staining shows lymphomononuclear cell infiltrate in the upper dermis with epidermotropism of singly distributed lymphocytes. (A) CD3; (B) CD4; (C) CD8; (D) CD30.

**Table 3.** Staging according to TNMB system of MF.

| Staging | Frequency | Percent |
|---|---|---|
| IA | 2 | 8 |
| IB | 9 | 36 |
| IIA | 2 | 8 |
| IIB | 3 | 12 |
| III | 2 | 8 |
| IVA | 2 | 8 |
| IVB | 5 | 20 |
| Total | 25 | 100.0 |

**Table 4.** CD4/CD8 ratio in patients with patch and erythrodermic stage.

| | Site | Range | Average |
|---|---|---|---|
| Erythroderma | Dermal | 3.1 - 5.7 | 4.4 |
| | Epidermal | 9.6 - 12.1 | 10.85 |
| Patch | Dermal | 1.2 - 3 | 2.01 |
| | Epidermal | 3.1 - 9.55 | 4.43 |

***Unusual Presentations*:** 1-Hypopigmented MF: In 3 patients the lesions were hypopigmented. One of them was an 18 years old female with 4 years duration of asymptomatic multiple hypopigmented patches. On examination she had 20 lesions distributed on her forearms, back, lower abdomen and inner thighs. The second patient was a 50 years old male with 7 years duration of asymptomatic hypopigmented patches (15 lesions) on the back and abdomen. The third patient was a 45 years old male with asymptomatic patches (11 lesions) on the back and abdomen for 10 years. In all cases the skin was abnormal in texture as the lesions were scaly and thickened and not just a hypopigmentation.

2-Hyperpigmented MF: One patient presented with hyperpigmented lesions.

3-Granulomatous MF: One patient presented with granulomatous lesions. This patient was a 77 years old male with 6 months duration of tumors (7 lesions) distributed on the right shoulder, anterior chest and bilateral inner thighs associated with palpable bilateral axillary and inguinal lymph nodes. Skin biopsy showed dense nodular lymphocytic infiltrates throughout the entire dermis with multinucleated histiocytic giant cells. The patient later on died due to visceral involvement (**Figure 5**).

4-Poikiloderma: Four patients present with poikilodermtous skin rashes in addition to the patch or plaque or tumor stage.

## 4. Discussion

Mycosis fingoides is very interesting T cell tumor and it is increasing all over the world including Iraq [6] [11]-[14]. Age of onset at the present study was 47.5 years while in the previous Iraqi study was 42.6 years but was comparable to other studies like USA 55 years; Europe 50 years and Korea 55 years [6] [11]-[14].

In the present work males were more than females with ratio 1.5:1 and this was comparable with other countries like USA 1.6:1 to 2:1; Europe 2:1 and Korea 1.4:1 [11]-[14].

Pruritus was the major symptoms among patients (84%) and this was the main presenting finding and was similar to other published studies [3] [11] [15].

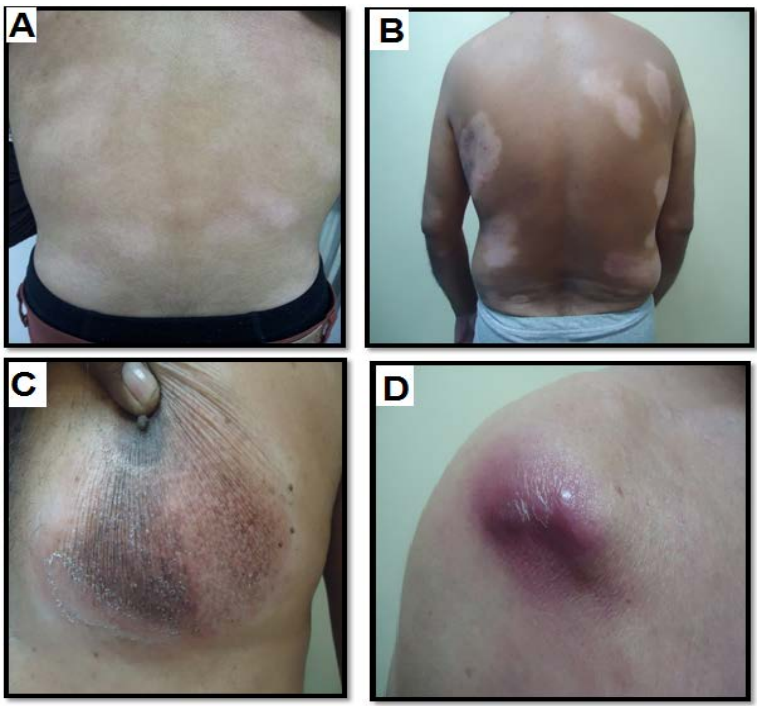


**Figure 5.** Clinical variants of MF. (A) Childhood onset MF: 18 years old age girl with these hypopigmented lesions for four years duration; (B) hypopigmented MF: Multiple hypopigmented macules and patches were noted on the back of 50 years old age male; (C) poikilodermatous MF on left breast of 55 years old male; (D) granulomatous MF: large mass in right shoulder of 77 years old male.

The patch alone was the commonest sign of disease as seen in 44% of cases while other patients presented with tumors (36%) single or multiple in addition to patch stage and 8% of patients was seen with erythroderma as part of Sezary syndrome. Palpable lymph glands were detected in 44% of patients at the time of diagnosis mainly in the axilla. This finding was much higher than previous Iraqi study where lymph gland enlargement was seen in 15% of cases while consistent with other reports [11] [15].

Fortunately in 36% of cases of MF presented with stage IB and this in agreement with the previous Iraqi study and this is could be explained to early presentation and diagnosis as most patients seen within 2 years of the disease but in contrast to previous Iraqi study where the time of presentation and diagnosis was 7.9 years [11]. This is probably related to more education of dermatologist about MF. While other studies from Europe and American countries, the stage of disease at time of diagnosis was mostly stage III and IV and this could be attributed to either to more aggressive disease or to the late establishment of diagnosis [12] [13] [16].

Scott *et al*. mentioned the ratio of CD4 to CD8 in patients with patch stage and erythrodermic stage. They put a range of the ratio as an aid to diagnosis of MF in patients with equivocal histopathological picture [17]. In this study all patients fall within this range (**Table 4**).

In Iraq, vitiligo often presents with stage I and stage II of depigmentation and the histopathology of these stages where described to be similar to early MF and even forming pautrier microabscess like [18]. Accordingly hypopigmented MF is rarely diagnosed and even might be questionable as both diseases stage I vitiligo and hypopigmentad MF are disease of children and respond to similar therapy and the prognosis is very good [18]-[20]. In the present work, hypopigmented MF seen in 3 (12%) of patients and these cases the skin is abnormal regarding the textures rather than just hypopigmentations in contrast with the stage I vitiligo where the skin is usually normal apart from pigment loss. This finding raises big question mark regarding the high frequency of hypopigmented MF in neighboring Arabian countries like Saudi Arabia (41.1%) and Kuwait (64%) and this high frequency of this variant might probably related to misdiagnosis with stage I vitiligo or a proper hypopigmented MF [21] [22].

Large anaplastic T cell lymphoma was detected in one patient and granulomatous MF was detected in one patient; these are rare variants [10] [17] [23].

## 5. Conclusion

In conclusion, MF in Iraqi population is commonly presented with patch stage (stage $I_B$) within a period of 2 years while the hypopigmented MF is not a common feature of the disease.

## Disclosure

This study is an independent study and not funded by a drug Companies.

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