Hypopigmented Mycosis Fungoides: A Clinicopathological Study of 10 Patients From Jordan (Middle East)

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ABSTRACT

Background: Hypopigmented mycosis fungoides (HMF) is a recognized variant of Mycosis fungoides (MF) that resembles several inflammatory dermatoses. Clinical and histopathological features of HMF must be well-characterized to ensure early recognition, especially that such information is lacking in Jordan.

Methods: We retrospectively reviewed medical records of 10 HMF patients, from 2015 to 2022. Clinical and histopathological features were extracted, reviewed, and summarized.

Results: Our cohort comprised 6 males and 4 females. Male: female ratio 3:2. Mean age at diagnosis was 21.2. The most common location was the trunk. Half reported mild itching. All were treated with NB-UVB ,90% achieved a complete response to treatment, one lost follow up.

All biopsy specimens displayed hyperkeratosis, epidermal hyperplasia, mild superficial dermal perivascular lymphoid infiltrate, and disproportionate spongiosis. Lining of atypical lymphocytes at the dermal-epidermal junction was encountered in 90% and papillary dermal fibrosis in 60%. Immunohistochemical staining was performed on 7 specimens, with 57.1% CD8 predominance and 42.8% CD4 predominance.

Conclusion: HMF in the Jordanian population shares histopathological and clinical features with published reports. Our report emphasizes the importance of obtaining a skin biopsy when considering HMF. A common theme was the variability in latency periods before diagnosis emphasizing the delay in diagnosis. Further data and techniques must be studied and integrated to ensure timely diagnosis.

Keywords: Mycosis fungoides, hypopigmented mycosis fungoides, Cutaneous Lymphoma,

T- Cell, Jordanian population

INTRODUCTION

Mycosis fungoides (MF) is a type of cutaneous T-cell lymphoma, a heterogenous group of extra-nodal non-Hodgkin's lymphomas that are characterized by the proliferation of monoclonal T-cells affecting the skin[1,2]. MF is considered the most common cutaneous T-cell lymphoma, according to the World Health Organization European Organization for Research and Treatment of Cancer (WHO-EORTC) classification[3]. MF has many clinicopathologic variants. Of those, well defined variants per the WHO-EORTC classification are folliculotropic, pagetoid reticulosis, and granulomatous slack skin. Other clinical variants include verrucous/hyperkeratotic, hyperpigmented, poikilodermatous, erythrodermic, bullous, vegetating, etc. Classic MF mostly affects individuals of older age and has a predilection for males. Initial presentation includes a gradual appearance of patches and plaques on nonexposed sites[4]. Early classical MF has been well acknowledged to resemble common dermatoses such as that of psoriasis and atopic dermatitis. More recently, this list has widened even further with MF's clinical and histological patterns overlapping with major inflammatory conditions[4,5]. Most notably, the hypopigmented variant of mycosis fungoides (HMF),is being recognized and emphasized as a disease entity that can be missed for several other hypopigmented skin disorders, such as vitiligo, pityriasis alba, Hansen disease, hypopigmented parapsoriasis en plaque, post inflammatory hypopigmentation, tinea versicolor, and sarcoidosis[6,7]. Presenting as flat plaques or hypopigmented patches that are covered in fine scales, HMF is most commonly encountered in children/adolescents and has a predilection towards individuals of dark skin complexion[8,9]. HMF lesions typically affect the trunk, buttocks, and limbs and are often asymptomatic or mildly itchy. Several studies have been published highlighting the clinical and pathological characteristics of this variant as it is being recognized worldwide. However, clinicopathologic identification is lacking in the Middle East, specifically Jordan. Since HMF is an important variant of MF that has a high incidence in the pediatric and juvenile populations, this paper offers insight into the clinical and histopathological features of HMF in the Jordanian population to facilitate timely diagnosis and management.

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METHODS

This is a retrospective study in which clinical and histopathological evaluation of patients was performed over a period of 7 years from 2015 to 2022; 48 patients were diagnosed with MF during this period of which 10 patients were identified as having HMF at the Jordan University and Al – Karak Governmental hospitals by at least two dermatologists following clinicopathologic assessment. Data regarding patients, their diagnosis, duration of onset, clinical characteristics, demographic characteristics of age and gender, and follow-up periods were retrieved from their files, reviewed, analyzed and summarized. The reported cases only had hypopigmented lesions without classic lesions of MF.

Response to treatment was assessed based on the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC) classification, namely, complete response (CR) (100% clearance of all lesions), partial response (PR) (50%-<100% response), and stable disease (SD) (<25% increase or < 50% clearance from baseline), maintained for at least one month, or progressive disease (PD) (>25% increase, loss of response)[10].

Biopsy specimens were obtained from all patients after taking consent. All were stained with Hematoxylin and Eosin (H&E), Immunohistochemical staining for CD3, CD4, and CD8 was done in some cases. The biopsies were viewed and interpreted by a dermatopathologist who confirmed the histopathologic diagnosis. T-cell Receptor (TCR) rearrangement studies were not performed as they were not available in the facility, however clinicopathological correlation was sufficient to reach a diagnosis. Statistical analysis was performed using IBM SPSS 25.

Ethical Considerations

The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Mutah University Ethics Committee on (29/06/2023), Reference Number:1162023.

RESULTS

Of the 10 patients being reported, 4 were females, 6 were males, with a male to female ratio of 3:2. Ages at diagnosis ranged from 4 to 45 with a mean of 21.2 years and a median of 13.5. Table 1 shows clinical characteristics of patients. In all patients, the most prevalent presenting symptom was related to skin discoloration (hypopigmented patches). All patients presented with lesions on their trunk, Fig. 1. Other common sites were the extremities. On Wood's light examination, two patients had a depigmented pattern of fluorescence (milky white fluorescence), as shown in Fig. 2, while the remaining patients had lesions with a hypopigmented pattern of fluorescence.

Half of the cohort complained of mild itching. Duration of skin lesions prior to diagnosis ranged from 3 months to 10 years with a mean of 26.2 months and a median of 18 months. Vitiligo was considered initially as a differential diagnosis in 7 patients (70%). Physical examination did not reveal any lymph node involvement in any of the patients. Abdomen and chest CT scans were done for 70% of patients with no evidence of extracutaneous involvement. 7 patients presented with TNM stage IA (T1/N0/M0) disease and 3 patients had stage IB (T2/N0/M0) disease.

All patients underwent treatment with narrow band ultraviolet B (NB-UVB) phototherapy.

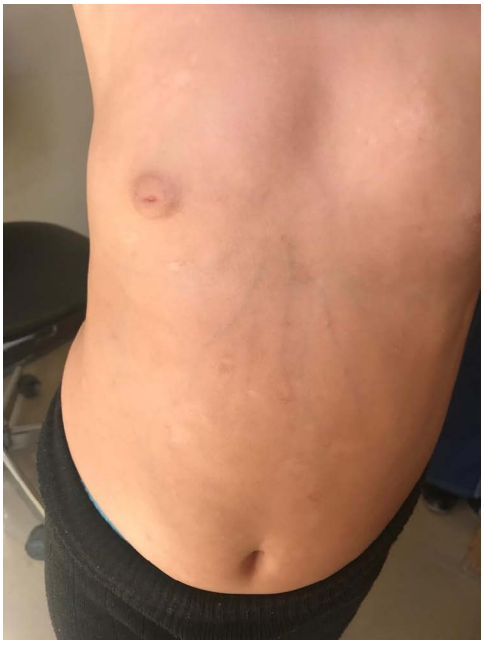

Figure 1. A 4-year-old female with hypopigmented patches and macules on the trunk.

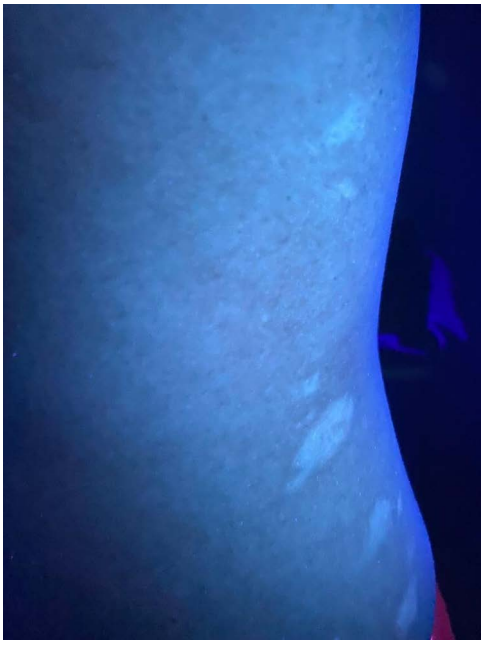

Figure 2. Wood's light examination showing milky white fluorescence of hypopigmented Mycosis Fungoides lesions in one of the cases.

9 patients (90%) achieved a complete response (CR), with one patient lost to follow-up. Patients were followed up for a duration that ranged from 2-6 years during which two patients relapsed and a complete response was re-achieved utilizing another course of NB-UVB.

Table 2 shows histopathologic features of biopsy specimens. On H&E staining, all biopsy specimens displayed epidermal hyperplasia and hyperkeratosis with a mild superficial dermal perivascular lymphoid cell infiltrate, and atypical lymphocytes (in the form of epidermotropism and/or haloed lymphocytes), Fig. 3. Lining of atypical lymphocytes at the dermal-epidermal junction was encountered in 9 patients (90%)

Table 1: clinical characteristics of the cohort.**CR: complete response (100% clearance of lesions, for at least a month), N/A: Not Available.**

ID	Age	Sex	Symptoms	Lesions Sites	Differential Diagnosis	Wood's Light	Duration Prior To Diagnosis	Response to treatment	Lymph nodes	Imaging studies (Abdomen Pelvis CT)	Clinical Stage
1	32	F	Mild itching, skin discoloration	Trunk, shoulders	Pityriasis alba, post inflammatory hypopigmentation	Hypopigmentation	2 years	CR	No enlargement	Negative	IA
2	4	F	Skin discoloration	Trunk, buttocks	Atopic eczema, vitiligo, hypopigmented mycosis fungoides	Hypopigmentation	6 months	CR	No enlargement	Not done	IA
3	7	M	Skin discoloration mild itching	Trunk, extremities	Atopic eczema, pityriasis alba, vitiligo, hypopigmented mycosis fungoides	Hypopigmentation	1 year	CR	No enlargement	Negative	IA
4	17	M	Skin discoloration	Trunk, thighs, buttocks	Vitiligo, hypopigmented mycosis fungoides	Depigmentation	8 months	CR	No enlargement	Negative	IB
5	45	F	Skin discoloration	Trunk, proximal extremities	Vitiligo, hypopigmented mycosis fungoides	Hypopigmentation	2 years	CR	No enlargement	Negative	IA
6	4	M	Skin discoloration	Trunk, neck, forehead	Vitiligo, hypopigmented mycosis fungoides	Depigmentation	3 months	CR	No enlargement	Not done	IA
7	45	M	Mild itching, skin discoloration	Trunk, proximal extremities	Hypopigmented mycosis fungoides, vitiligo	Hypopigmentation	10 years	CR	No enlargement	Negative	IB
8	43	M	Very mild itching, skin discoloration	Trunk, proximal extremities	Hypopigmented mycosis fungoides, vitiligo	Hypopigmentation	2 years	CR	No enlargement	Negative	IB
9	10	M	Mild itching, skin discoloration	Trunk, extremities	Atopic eczema	Hypopigmentation	3 years	CR	No enlargement	Negative	IA
10	5	F	Skin discoloration	Trunk, upper thighs	Hypopigmented mycosis fungoides, atopic eczema	Hypopigmentation	5 months	N/A No follow-up	No enlargement	Not done	IA

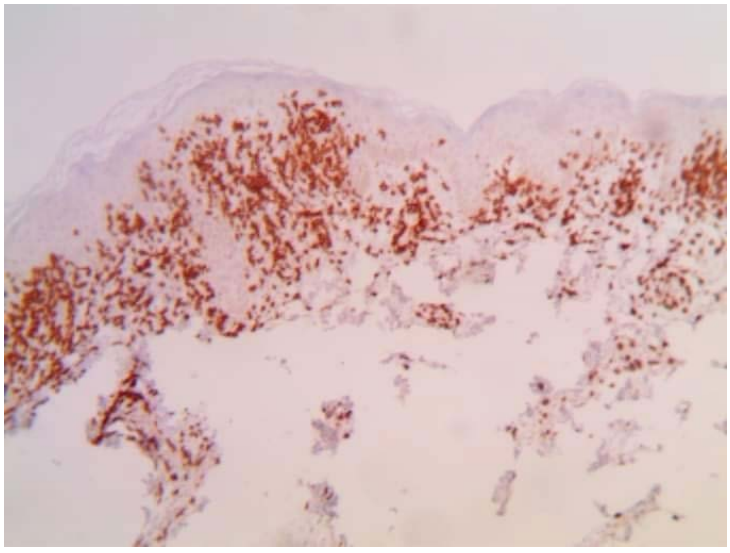

Figure 3. H&E (x40), displaying prominent epidermotropism of atypical lymphocytes, haloed lymphocytes, disproportionate spongiosis and papillary dermal fibrosis.

Table 2. Histopathological features of the cases.

ID	Epidermal changes	Dermal infiltrates	Atypical lymphocytes in the epidermis	Lining of atypical lymphocytes at the dermo-epidermal junction	Disproportional spongiosis	Papillary dermal fibrosis	Pautrier microabscess	CD4/CD8
1	Epidermal hyperplasia, Hyperkeratosis, Parakeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	+	-	CD8 predominant
2	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	-	-	CD8 predominant
3	Epidermal hyperplasia, Hyperkeratosis, Parakeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	+	-	Not done
4	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	-	-	CD8 predominant
5	Epidermal hyperplasia, Hyperkeratosis, Focal parakeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	+	-	Not done
6	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	-	-	CD8 predominant
7	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	-	+	+	+	Not done
8	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	+	-	CD4 predominant
9	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	+	-	CD4 predominant
10	Epidermal hyperplasia, Hyperkeratosis	Mild superficial perivascular lymphoid cell infiltrate	+	+	+	-	+	CD4 predominant

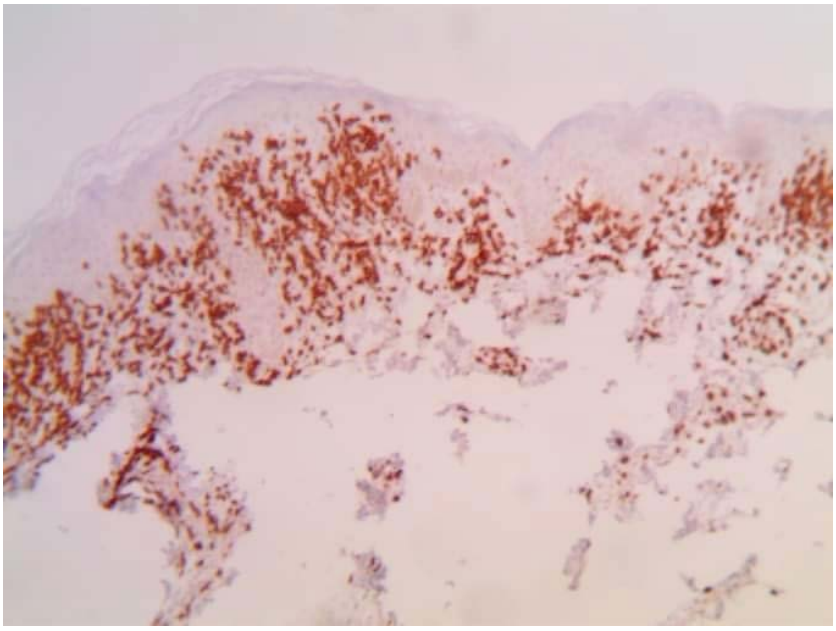

Figure 4. CD8 immunostaining (x10), displaying the predominance of CD8 positive T- lymphocytes.

of biopsy specimens. We also noted disproportionate spongiosis (a minimal degree of spongiosis in relation to the degree of epidermal infiltrate of lymphocytes), in all patients and papillary dermal fibrosis was evident in 6 cases (60%), Fig. 3. Pautrier microabscesses were identified in 3 specimens (30%). Immunohistochemical staining was performed on 7 specimens, of which, CD8 predominance was evident in 4 (57.1%) while CD4 predominance was encountered in 3 (42.8%), as displayed in Fig. 4 below.

DISCUSSION

HMF is an uncommon variant of MF that presents with hypopigmented patches on the trunk and extremities, especially in children. It is more common among individuals with dark skin phototypes[9]. The loss of pigmentation is attributed to the decrease in the number of melanocytes in the affected skin. This process pertains to the cytotoxic effects of the CD-8$^+$ T-cells[11,12]. Hypopigmentation in this variant has been proposed as a potential indicator of an active immune response. Specifically, an anti-tumor immune response against malignant T-cells, regardless of phenotype[12], which perhaps contributes to the more favorable prognosis of this variant. Literature regarding this variant is lacking in the Jordanian population. Hence, our study highlights clinicopathologic features of 10 HMF Jordanian patients in order to track and identify any distinct features to gain more insight on this condition.

Previous studies in Jordan describing MF have reported clinicopathological characteristics in a series of 7 children and adolescence and 63 cases ages 11 – 80. Of which, 57% and 11% had features correlating with the hypopigmented variant, respectively, according to reports by Al-Tarawneh[13,14]. Although studies are yet to uncover the prevalence of HMF in Jordan, these reports, along with ours, highlight that it is certainly common among the pediatric population. Furthermore, both studies have also highlighted the wide differential diagnoses that may be considered with initial presentations of HMF, these include eczema, post-inflammatory hypopigmentation, tinea versicolor, and vitiligo, which was also the case in our study, with vitiligo being the most common alternative diagnosis considered in 7 of our patients.

Diagnosing HMF is indeed challenging in most scenarios as it highly overlaps with many diseases that initially present with hypopigmented lesions. The lack of sufficient criteria or the presence of atypical features that are inconsistent across reports further adds to the complexity of the diagnosing process. Moreover, HMF usually has an indolent nature that often leads to many situations of under- or over-diagnosis[15]. Patraquim et al. and Gameiro et al. reported two children aged 5 and 8 years, respectively who were treated with emollients as a benign dermatosis/pityriasis alba before the biopsy results were consistent with a diagnosis of HMF[16,17]. Because HMF lacks clear-cut symptoms and signs and mimics a broad category of other benign dermatoses, the diagnosis often times requires a high index of suspicion and a close inspection of skin biopsy with multiple biopsies needed to reach a definitive diagnosis. These implications are even more critical considering the diagnosis intervals displayed in our results ranging from 3 months to 10 years. Previous studies report numbers reaching as high as 30 years in some cases with an average of 2.5 biopsies to reach a diagnosis[18], this highlights the importance of long-term follow-up and re-biopsies for patients that are suspected of having HMF.

Recent studies have highlighted the importance of examining the basement membrane thickness and proposed it as a differentiating factor of HMF compared to other conditions[19,20]. Penitent to our results, a report by Abdelkader compared the basement membrane thickness between 21 HMF patients and 25 non-HMF cases with hypopigmented lesions using Periodic acid–Schiff (PAS) stained biopsy specimens. The results displayed that the cut-off value for detecting HMF was a thickness greater than 33µm with a sensitivity and specificity of 85.7% and 96%, respectively[20]. Using the basement membrane thickness could be a viable option to differentiate HMF from mimickers when in doubt[19,20].

Narrowing differential diagnoses may be aided by integrating modern techniques in practice. Along with high clinical suspicion, for example, Liu et al. demonstrated excellent utility for reflectance confocal microscopy in differentiating HMF and vitiligo[21], which could represent a valuable tool that might help distinguish HMF from its inflammatory counterparts. Other tools that are more commonly used in the clinical workflow could also be utilized like that of the dermoscope. Reports that studied and identified architectural features of this variant have described a patchy, amorphous, white-pink area with a loss of pigment network, as reported by Nakamura and colleagues[22], perhaps this can also be integrated into the diagnostic armamentarium when faced with HMF cases, facilitating early diagnosis, management, and raising the index of clinical suspicion.

Our cohort was comprised of 60% male patients with an average age at diagnosis of 21.2 years. Some studies have reported similar results with regards to male-to-female distribution[23,24]. Our patients are diagnosed at a relatively young age which is in line with the literature; Alhumidi reported a mean age of 17 years and in Shi et al's report of 32 Chinese patients with HMF the mean age at diagnosis was 18 years[24,25].

In our cohort, the most common site of involvement was the trunk, involved in 100% of patients. The notoriety of involvement of the trunk and extremities is noticeable across studies which echoes well with our results. According to Alhumdi et al., the most common sites of involvement were the upper and lower extremities (100%) followed by the trunk (76%)[25]. Amorim et al. noted that non-photo exposed areas were involved in 100% of their cases[18]. In Domínguez-Gómez et al. report, the trunk (89.6%) and lower limbs (89.6%) were the most affected sites, Khopkar et al also reported that the back and proximal extremities were mostly involved[23,26]. Lesions affecting these sites should prompt high suspicion into considering HFM as a differential diagnosis when encountered, and there should be a lower threshold to performing biopsies in order to prove the diagnosis early on and to repeat biopsies when necessary.

Abdomen and Pelvis CT scans were performed in 7 of our patients and clinical examination for all, none were found to have any visceral or nodal involvement at the time of diagnosis. This was similarly noted in Khopkar et al's cohort of 15 Indian HMF patients, thus emphasizing this variant's more favorable prognosis when compared to classic MF or other variants[26]. Although the diagnosis is often delayed, it is usually diagnosed at an early stage and remains dormant for years, rarely progressing beyond stage IB[27].

We reported the histologic features of all our cases. Regarding epidermal changes, all biopsies displayed epidermal hyperplasia, hyperkeratosis, and disproportionate spongiosis. Papillary dermal fibrosis was evident in 6 of our cases (60%). In a report by Khopkar et al., 40% of histologic biopsies from 15 HMF patients displayed epidermal hyperplasia which is lower than our findings. Other findings present in their cases were thickened or wiry collagen bundles in 60% of specimens and disproportionate spongiosis in 14 cases, indicating their significance in HMF biopsies[26.]

Pautrier microabcsesses were identified in only 30% of our biopsy specimens, similarly they were encountered in 29% of Hassab-El-Naby

et al's Egyptian patients and Khopkar et al. reported this finding in 40% of cases (6/15)[26,28.] This indicates that it is not a consistent finding.

Biopsies displayed the presence of lymphocytes at the dermo-epidermal junction in 90% of our patients, it was the most frequent finding in all the cases reported by Alhumidi[25]. Similarly, this histopathologic finding was encountered in 15/15 patients as described by Khopkar and colleagues[26]. The most consistent feature in terms of inflammatory infiltrate.

In regard to immunohistochemical staining pattern, Shi et al. reported a predominance CD8 in 63.3% of cases, Rodney et al. also noted a CD8 predominance 58.3% of patients, this was also noted by Khopkar et al as 8/10 patients had CD8 predominance in the infiltrate[6,23,24]. Moreover, in Jaque et al's report examining the phenotypic variants of mycosis fungoides in relation to immunohistochemical analysis and staining patterns, the hypopigmented variant comprised 2.4% of the CD4+ group vs. 20.6% of the CD8+ group which is all in concordance with our results where CD8 predominance evident in 57.1%, proving that the dominance of CD8+ cells is quite a consistent feature spanning several nations and populations[29]. This cytotoxic immunophenotype contributes to the more favorable prognosis of this variant when compared to classic MF.

Treatment options for HMF are mainly related to phototherapy, particularly photochemotherapy[30]. The literature delineates the benefit of using it as a first-line therapy because, in the majority of reported cases, it ensured full remission[18,23,30]. However, no guidelines exist regarding its use for this indication. Our patients were all treated with NB-UVB phototherapy with 90% displaying a complete response to treatment. Phototherapy has proven to be very effective across many Asian patients[30,31]. Other treatment modalities have also showed results with high remission rates, such as topical nitrogen mustard, and topical steroid[24]. Regardless of treatment modality, it is crucial to emphasize the importance of long-term follow up and treatment maintenance since recurrence rate in HFM is relatively high even after multiple successful treatment sessions[23].

CONCLUSION

In conclusion, Hypopigmented mycosis fungoides (HMF) is an uncommon variant of mycosis fungoides that primarily affects children, adolescents, and people with darker skin phototypes and has a more favorable prognosis compared to other variants. The diagnosis of HMF is rather challenging and delayed due to its indolent nature and resemblance to other benign dermatological conditions. Treatment options for HMF mainly involve phototherapy, particularly photochemotherapy, which has shown promising results in achieving remission in our study. Long-term follow-up and treatment maintenance are essential. HMF profiles described within our study share features with those mentioned in other reports. Skin biopsies are vital in diagnosing and differentiating HMF from benign counterparts. As is evident in our report and throughout the literature; the lining of atypical lymphocytes at the dermal-epidermal junction is a consistent histopathological feature and clue to diagnosis. Future research should aim to recruit more cases to accurately estimate the prevalence of HFM in the Jordanian population, perhaps delineating more clinicopathologic features aiding in diagnosis and recognition. The utility of various methods aiding to narrow the differential diagnoses that may overlap with HFM warrants further investigations, such as the utility of the basement membrane thickness and reflectance confocal microscopy.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 06-06-2024

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