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Suspicion of Mycosis Fungoides: A Nightmare for Dermatologists and Pathologists

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Abstract

Objective: Diagnosing mycosis fungoides (MF) poses a challenge both clinically and pathologically. In its early stages, MF may exhibit minimal changes, leading to potential misdiagnosis as benign inflammatory dermatoses. This study aimed to evaluate the clinicopathological features of cases where there is clinical suspicion of MF.

Methods: A total of 254 consecutive patients with suspected MF were included in the study. Clinical findings and pathology reports were retrospectively obtained from hospital records, and the clinicopathological features were subjected to statistical analysis.

Results: The median age of the study participants was 39.4 ± 19.2 years old (range: 0-85), with 52% being male. Clinical erythematous lesions were significantly more common among participants whose MF had been identified as the initial diagnosis based on clinical preliminary diagnoses (P = .02). Histomorphological MF diagnosis was statistically significant in clinically erythematous lesions, while histomorphological suspicion for MF group was more common in the clinical "other" group (P = .001, P = .03). Hyperchromasia, cytoplasmic halo, and atypical intraepidermal collections of lymphocytes were statistically more prevalent in histomorphological MF diagnoses (P < .001).

Conclusion: Although the clinicopathological spectrum of MF diagnosis may vary across disease stages, our study demonstrates the importance of both clinical and pathological examination of erythematous lesions for MF. Compared to other pathological criteria for MF, changes in lymphocyte size and shape may have less significance in determining MF's pathological suspicion. The best approach for diagnosing MF is to collate accurate data to avoid misdiagnosis.

Keywords: Diagnosis, lymphoma, mycosis fungoides, skin, suspicion

Introduction

Mycosis fungoides (MF) accounts for approximately 50% of primary cutaneous T-cell lymphoma diagnoses, making it the most common subtype.[1] Potential risk factors include genetic predisposition, as well as exposure to various allergens and chronic skin disorders.[2] Although MF predominantly affects adults, it can also occur in children and adolescents.[3] The gender distribution ratio (male to female) is 2 : 1.[4]

Early-stage MF exhibits indolent behavior, progressing slowly from patches to plaques and tumors.[5] In their early forms, MF can resemble other benign inflammatory dermatoses both clinically and histomorphologically.[6]

Histomorphologically, MF is characterized by "atypical small to medium-sized T-cell lymphocytes with a cerebriform nucleus in the papillary dermis, accompanied by infiltration into the epidermis (epidermotropism)."[1] Differentiating MF from its clinical mimics requires routine dermatopathological evaluation.[7] In this study, we aimed to determine the clinicopathological features of cases where the clinical suspicion of MF was a factor. Because histomorphology is known as a critical point for MF diagnosis, we also aimed to clarify the diagnosis of "suspicion of MF" both clinically and pathologically.

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Methods

This study was approved by the Ethics Committee of Health Sciences University (Approval No: 2021.11.251, Date: December 20, 2021). Written informed consent was obtained from all participating patients.

A total of 254 consecutive patients and their skin biopsies, performed by the Dermatology Department and evaluated by the Pathology Department between June 2020 and August 2021, were included in the study. Clinical and pathological data were retrospectively collected from hospital records and pathology reports. Patient information, including age, sex, biopsy location, and preliminary clinical diagnoses, was obtained from hospital records. Preliminary clinical diagnoses were grouped as follows: group 1 (erythematous scaly patch, papule and plaque, tumor, erythroderma), group 2 (petechiae, purpura), group 3 (pigmentation disorder), group 4 (follicular involvement), and group 5 (other, such as alopecia, atrophy/poikiloderma, nonspecified lesions). In cases where patients displayed multiple clinical patterns, they were categorized as either "single" or "multiple" clinical appearances. Due to some patients having multiple clinical appearances, 1 patient may be placed in more than 1 group. Patients diagnosed with MF in the preliminary clinical diagnoses were classified into groups based on the order of diagnosis: "first," "second," "third," or "fourth and above."

Pathology reports were examined to identify histopathological features in the biopsies. Hematoxylin and eosin-stained slides of all biopsies were reviewed and scored. The presence or absence of atypical features in the lymphocytes of the epidermis was categorized based on their size, irregularity, hyperchromasia, cytoplasmic halo, and atypical intraepidermal collections. They were scored as absent (0) or present (1). These features were compared to relatively normal dermal lymphocytes, and inadequate or repetitive biopsy samples were excluded from the study.

Statistical analysis was performed using the Statistical Package for the Social Sciences Statistics software for Windows, version 22.0 (Chicago, Ill, USA). Descriptive statistical methods, including mean, median, minimum, maximum, percentage, frequency, and standard deviation, were used to evaluate the data. The Pearson's chi-square, Fisher's exact, and Freeman–Halton tests were employed to analyze clinical and pathological parameters. Statistical significance was determined as $P < .05$.

Results

Among the cases, 52% (n = 132) were male, with a mean age of 39.4 ± 19.2 years (range: 0-85 years). The most common biopsy location was the trunk (44%, n = 111), followed by the lower extremity (33%, n = 85), upper extremity (17%, n = 44), and head and neck (6%, n = 14).

Multiple clinical patterns were observed in 17% (n = 43) of the patients. Group 1, comprising 58% (n = 148) of cases, was the most frequent clinical pattern, followed by group 3, which accounted for 34% (n = 86) of cases. In the preliminary clinical diagnoses, MF was most commonly the initial diagnosis (31%, n = 78), while the least common was a fourth and above diagnosis (15%, n = 39). The frequency of a single clinical pattern was higher in cases with a fourth and above clinical preliminary MF diagnosis ($P = .02$).

Regarding histomorphological findings and their association with MF, 84% (n = 212) of patients showed no findings consistent with MF, while 9% (n = 24) exhibited findings consistent with MF, and 7% (n = 18) had findings suspicious for MF.

Group 1 was significantly more common in the first diagnosis of MF within the preliminary clinical diagnoses ($P = .02$). The histomorphological diagnosis of "consistent with MF" was statistically significant in group 1 compared to the histomorphological diagnoses of "negative for MF" and "suspicious for MF" ($P = .001$) (Table 1). Figure 1 illustrates the histomorphological and clinical appearance of early-stage MF in group 1, while Figure 2 shows the late stage. On the other hand, the histomorphological diagnosis of "suspicious for MF" was statistically higher in clinical group 5 compared to the histomorphological diagnosis of "consistent with MF" ($P = .03$). Figures 3 and 4 present atrophic and alopecic clinical lesions with their corresponding histomorphological suspicion for MF, respectively.

In the histopathological evaluation, all atypical lymphocyte features were significantly more common in the "consistent with MF" diagnosis compared to the "negative for MF" diagnosis ($P < .001$). Hyperchromasia, cytoplasmic halo, and atypical intraepidermal collections of lymphocytes were significantly more common in the "consistent with MF" diagnosis compared to the "suspicious for MF" diagnosis ($P < .001$). There was no significant difference in the size changes and irregularity of lymphocytes between these 2 groups (P = NS (not significant)) (Table 2) (Figure 5).

Discussion

Early diagnosis of MF is often challenging. While immunohistochemistry and molecular methods can aid in diagnosis, not all institutions have access to these techniques. Therefore, histopathological examination remains the primary means of diagnosis. In this study, we have highlighted the histopathological features of MF suspicion, along with the clinical characteristics of the disease.

Our findings indicate that a single clinical pattern is less likely to raise clinical suspicion for MF. Unless a patient displays isolated lesions, those diagnosed with MF usually exhibit multiple clinical types.[8]

The medical literature reports several clinical variants of MF.[9] The presentation of the disease varies across different stages, with

Table 1. Comparison of Clinical groups, Clinical Preliminary Diagnosis for Mycosis Fungoides, and Pathological Diagnosis of Mycosis Fungoides

	Clinical Groups*					
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	***P***
Clinical Preliminary Diagnosis for Mycosis Fungoides						
First diagnosis	56	4	23	12	14	[a]P = **.02****
Second diagnosis	42	12	20	10	10	
Third diagnosis	30	5	24	12	2	
Fourth/above diagnosis	20	2	19	1	1	
Pathological Diagnosis of Mycosis Fungoides						
Negative for mycosis fungoides	113	21	78	29	22	[b]P = **.001****
Suspicious for mycosis fungoides	13	2	6	2	0	
Consistent with mycosis fungoides	22	0	2	4	5	

Values in bold indicate statistical significance.
*Group 1 (erythematous scaly patch, papule and plaque, tumor, erythroderma), group 2 (petechiae, purpura), group 3 (pigmentation disorder), group 4 (follicular involvement), and group 5 (other, i.e., alopecia, atrophy/poikiloderma, nonspecified lesions).
**$P < .05$.
[a]Pearson chi-square test.
[b]Freeman–Halton test.

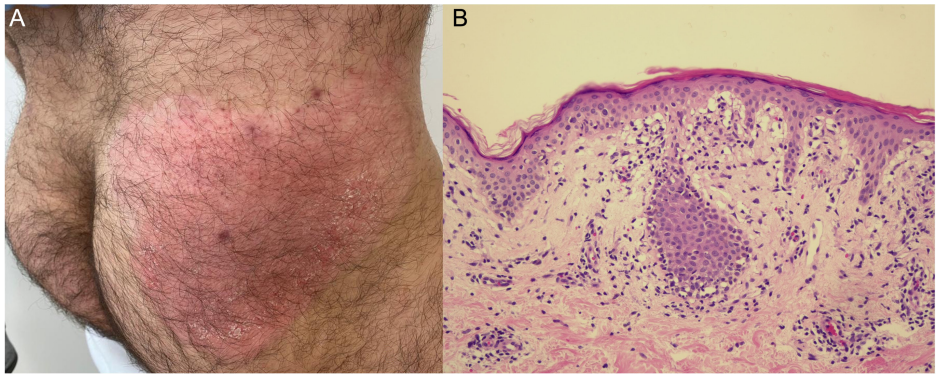

Figure 1. Erythematous scaly plaque (clinical group 1) in the gluteal area (A), histomorphological "consistent with MF" group with atypical intraepidermal collections, nuclear irregularity, perinuclear halo, hyperchromasia, and size changes (×20) (B).

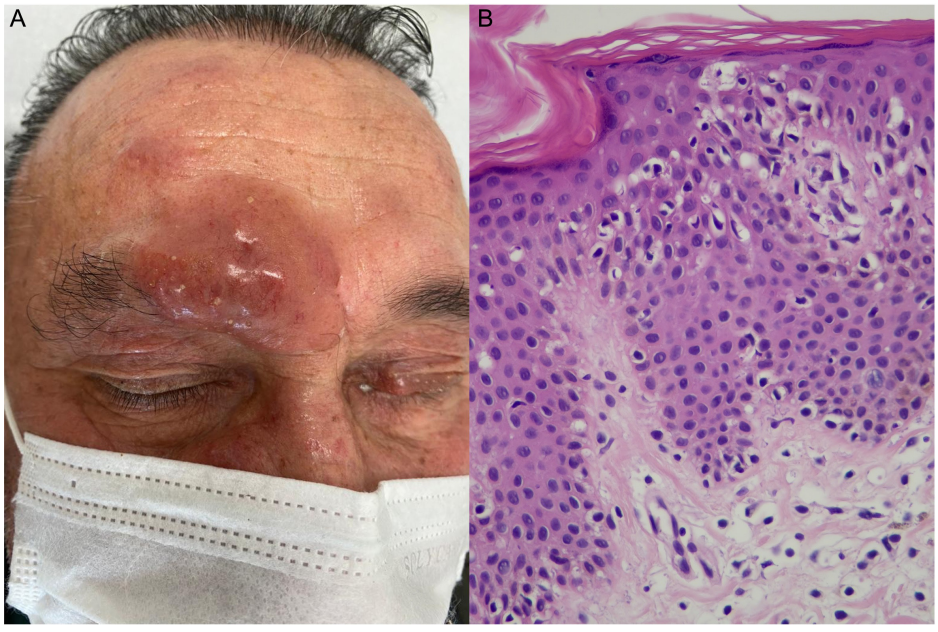

Figure 2. Tumoral lesion (clinical group 1) on the eyebrow (A), histomorphological "consistent with MF" with atypical intraepidermal collections, nuclear irregularity, perinuclear halo, hyperchromasia, and size changes (×40) (B).

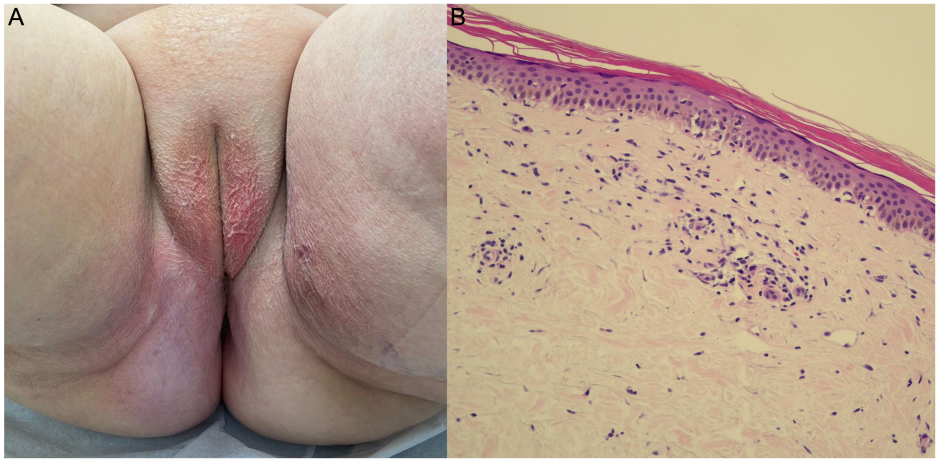

Figure 3. Atrophic plaque (clinical group 5) on the vulva (A), histomorphological "suspicion of MF" group with nuclear irregularity and size changes (×20) (B).

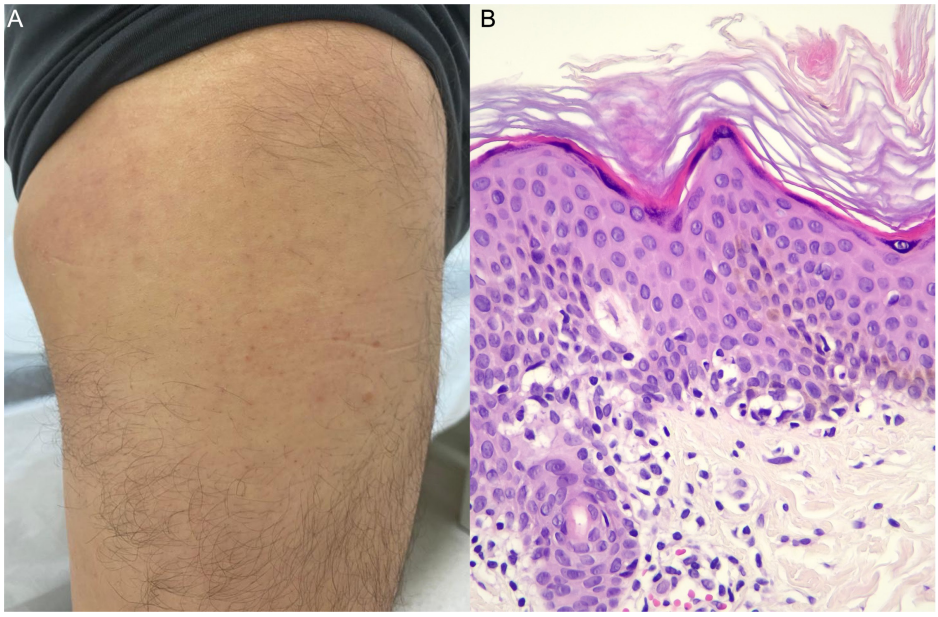

Figure 4. Alopecia (clinical group 5) on the outside of the thigh (A), histomorphological "suspicion of MF" group with nuclear irregularity and size changes (×40) (B).

Table 2. Comparison of the Histopathological Atypical Features of Lymphocytes Between Suspicious for Mycosis Fungoides and Consistent with Mycosis Fungoides Groups

	Histopathological Diagnosis for MF		
Histopathological Atypical Features of Lymphocytes	**Suspicious for Mycosis Fungoides (n = 18)**	**Consistent with Mycosis Fungoides (n = 24)**	***P***
Hyperchromasia			
Absent	11	3	[a]*P* = **.001***
Present	7	21	
Cytoplasmic Halo			
Absent	13	9	[a]*P* = **.02***
Present	5	15	
Intraepidermal Atypical Lymphocytes			
Absent	17	9	[a]*P* < **.001***
Present	1	15	
Size Changes			
Absent	1	3	[b]*P* = NS**
Present	17	21	
Nuclear Irregularity			
Absent	3	1	[b]*P* = NS
Present	15	23	

Values in bold indicate statistical significance.
[a]Pearson's chi-square test.
[b]Fisher's exact test.
*$P < .05$
**Not significant.

erythematous lesions being the earliest manifestation.[10] During this early phase, histopathological diagnosis of MF is often challenging, as it may display overlapping features with inflammatory dermatoses.[11] As expected, we found that erythematous lesions were the most clinically suspicious for MF. Although the pathological changes in these lesions can be subtle, our histopathological evaluation supported the notion that they are useful for making a diagnosis.

The "suspicious for MF" histopathological diagnosis is a key point in our study. Besides the clinical challenges associated with diagnosing MF, it can also be difficult to recognize in histopathological evaluations.[12] The term "suspicious for MF" is typically used for histomorphological features that are not clearly indicative of MF in early cases or resemble exaggerated inflammatory dermatoses.[13] These cases pose a diagnostic challenge due to the presence of ambiguous findings.[14]

In our study, the histopathological "suspicious for MF" diagnosis was more prevalent in the "other" clinical group, which included atrophy/poikiloderma, alopecia, and nonspecified lesions. The presence of atrophic/poikilodermatous changes in non-sun-exposed areas and well-defined alopecic patches may raise clinical suspicions of MF.[10,15] These rare presentation forms of MF do not always exhibit clear histomorphological distinctions from benign dermatoses. It is thus expected to find suspicious histopathological findings for MF in the "other" group of clinical lesions.

In evaluating the histopathological "suspicious for MF" diagnosis, we did not observe any differences in lymphocyte size and irregularity compared to patients with a histopathological diagnosis of MF. However, we demonstrated that hyperchromasia, cytoplasmic halo, and atypical intraepidermal collections of lymphocytes are highly indicative of MF.

Numerous research studies have been conducted on the definitive diagnosis of early MF, but a consensus on specific pathological criteria has yet to be reached.[16,17] In the first study on early MF in 1979, Sanchez and Ackerman emphasized the importance of early recognition and differentiation of MF from its benign inflammatory

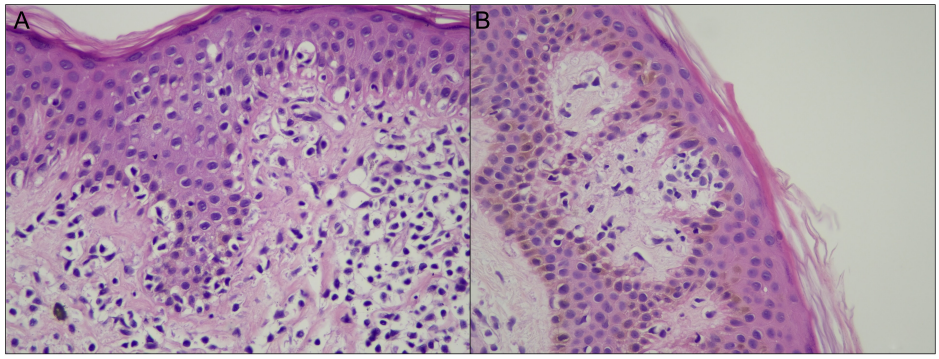

Figure 5. Histomorphological diagnosed mycosis fungoides with hyperchromasia, cytoplasmic halo, atypical intraepidermal collections, size changes, and irregularity of lymphocytes (×40) (A). Histomorphological suspicion of mycosis fungoides with size changes and irregularity of lymphocytes (×40) (B).

counterparts.[18] Ackerman later defined 4 parameters for the histopathological diagnosis of early MF in 1985: epidermotropism, larger epidermal lymphocytes compared to dermal lymphocytes, single lymphocytes along the basal layer, and dermal fibrosis with lichenoid lymphocytic infiltrate.[19]

Santucci et al[16] reported that the presence of medium or large lymphocytes with irregular-shaped nuclei in the epidermis or dermal sheets was the most significant histopathological criterion for MF. Similarly, another study suggested that the presence of irregularly contoured lymphocytes and epidermal lymphocytes larger than those observed in benign inflammatory dermatoses is suggestive of an MF diagnosis.[10] Both studies emphasized the diagnostic value of larger and irregular-shaped lymphocytes. However, Sanchez and Ackerman argued that nuclear size and shape might not be representative of early MF. It should be noted that there is no cut-off value for the nuclear size and shape of dermal and epidermal lymphocytes in inflammatory dermatoses. Moreover, due to variations in laboratory conditions, objective assessment, particularly regarding nuclear size, remains challenging.

Our findings regarding the definitive diagnostic criteria for MF, such as hyperchromasia, cytoplasmic halo, and atypical intraepidermal collections of lymphocytes, align with the existing literature. In contrast to studies that defined nuclear size and irregularity as specific criteria for MF suspicion, we did not consider these criteria distinctive. Although Sanchez and Ackerman's findings are considered outdated, our study similarly showed that nuclear size and irregularity are not specific criteria for MF diagnosis.

In conclusion, we have demonstrated the clinicopathological characteristics of MF suspicion. Certain features, such as the presence of multiple erythematous lesions or specific pathological criteria like hyperchromasia, cytoplasmic halo, and atypical intraepidermal collections of lymphocytes, can aid in making an MF diagnosis. However, the clinicopathological correlation remains the essential aspect of diagnosing MF—a challenging disease to evaluate both clinically and pathologically.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Health Sciences University (Approval No: 2021.11.251, Date: December 20, 2021).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept – B.Ç.G.; Design – B.Ç.G., C.C.; Supervision – F.K.Ç.; Resources – B.Ç.G., C.C.; Materials – B.Ç.G., C.C.; Data Collection and/or Processing – B.Ç.G., C.C., F.K.Ç.; Analysis and/or Interpretation – B.Ç.G., C.C., F.K.Ç.; Literature Search – B.Ç.G., C.C., F.K.Ç.; Writing Manuscript – B.Ç.G., C.C.; Critical Review – F.K.Ç.

Declaration of Interests: The authors have no conflict of interest to declare.

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