DOI: htttps://doi.org/10.3126/njdvl.v23i2.84122

Unveiling Mycosis Fungoides: The Diagnostic Challenge Requiring Multiple Skin Biopsies

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Abstract

Mycosis fungoides is a rare malignant skin neoplasm. It is the most prevalent primary cutaneous T-cell lymphoma. Hypopigmented mycosis fungoides, a variant, has been observed in Asian and dark-skinned individuals. We present a case of a twenty-four-years-old Nepalese woman with multiple asymptomatic hypopigmented macules on her arms, thighs, abdomen and back. The patient was treated with topical steroids, oral steroids, and topical psoralen with UVA phototherapy for suspicion of vitiligo and Pityriasis lichenoides chronica. After three biopsies, histopathology revealed an epidermis with focal subtle vacuolization in junctional zone and epidermotropic small and slightly enlarged lymphocytes with irregular nuclei. Immunohistochemistry showed increased CD4:CD8 ratio. Hypopigmented mycosis fungoides occurrence is infrequent not only in our region but also in Western literature. Recognizing hypopigmented mycosis fungoides as a rare condition and including it in the differential diagnosis of hypopigmented dermatological conditions can aid physicians in early diagnosis and reduce morbidity and mortality through appropriate management and care.

Keywords: immunohistochemistry, lymphoma, mycosis fungoides, skin neoplasm

Introduction

Mycosis Fungoides (MF) is the most common form of cutaneous T-cell lymphoma, accounting for approximately 50% of all primary cutaneous lymphomas.[1] Classic MF is characterized by large erythematous patches that may evolve into plaques, and less commonly tumors or extracutaneous involvement.[2] Early stage MF often mimics benign inflammatory dermatoses such as eczema or psoriasis, making clinical diagnosis challenging.[3] Histopathological features in early MF can be subtle and non-specific, often resembling chronic dermatitis.[4] Given the variability in clinical and histological presentations, multiple skin biopsies over time are often required to confirm the diagnosis, especially in the early stages. Repeated biopsies increase the likelihood of detecting characteristics histopathological features, such as epidermotropism and atypical lymphocytes.[5] Here, we present a case of hypopigmented MF who has undergone multiple biopsies due to diagnostic dilemma.

Funding: None
Conflict of Interest: None

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Case Report

Here we present a case of twenty-four-years-old female who was diagnosed with Mycosis Fungoides after three repeated biopsies after ten years of development of symptoms. The patient presented with the persistent, pruritic skin lesions over the different parts of the body including abdomen, dorsum of both hands, evolving over last ten years. She was initially clinically diagnosed and treated as a case of scabies and prurigo nodularis. Empirical treatment with topical corticosteroids and antihistamines provided temporary relief without complete resolution. A few months later, she developed hypopigmented macules and patches over the inner aspect of left arm, for which she was treated multiple times as a case of Pityriasis versicolor and pre-vitiligo. With the persistence of the lesions, the first skin biopsy was done from the lesion of arm. The findings

Date of Submission: 5th September 2025
Date of Acceptance: 28th September 2025
Date of Publication: 20th October, 2025

How to cite this article
Shrestha A, Chapagain L, Khadka A, Baral S, Shrestha DP. Unveiling Mycosis Fungoides: The Diagnostic Challenge Requiring Multiple Skin Biopsies. NJDVL 2025; 23(2): 64-66. https://doi.org/10.3126/njdvl.v23i2.84122

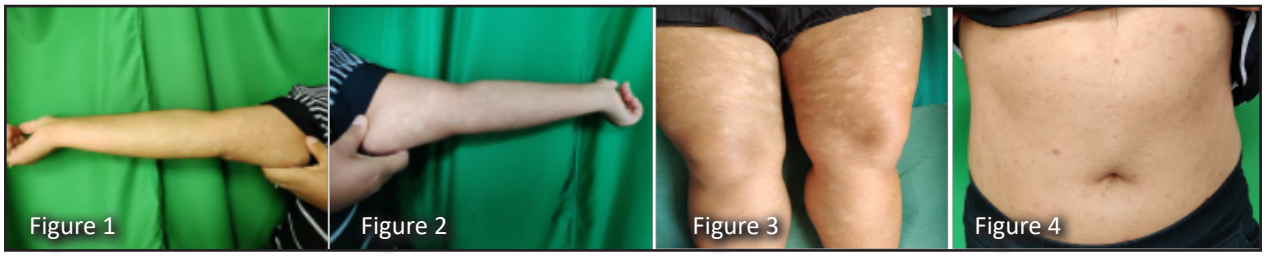

Figure 1,2,3,4: Multiple ill-defined hypopigmented macules over bilateral upper and lower extremities, abdomen; few erythematous papules scattered over abdomen

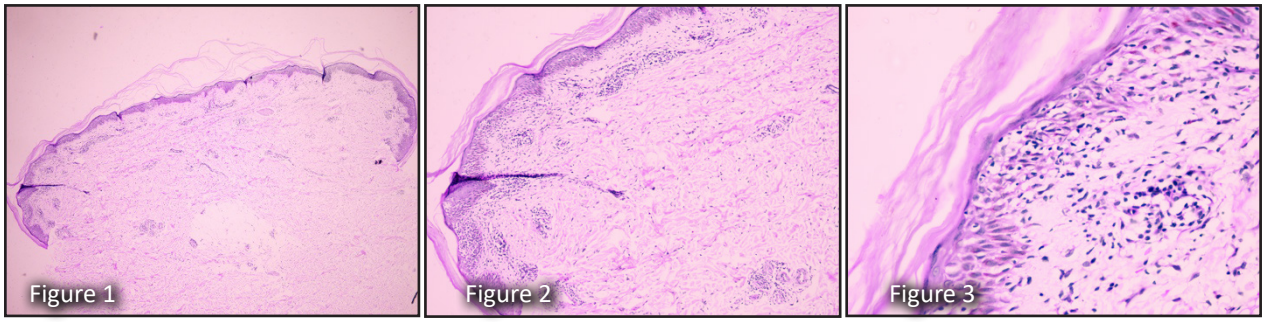

Figure 5,6,7(H&E stain, 4x,10x,40x respectively): Presence of epidermotropic lymphocyte infiltration, epidermis with focal vacuolar interface dermatitis and exocytosis of small and slightly enlarged lymphocytes with cerebriform nuclei

on the histopathological examination showed non-specific features like mild spongiosis with lymphocytic exocytosis, mild superficial vascular lymphocytic infiltrate with pigmentary incontinence, reported as subacute spongiotic dermatitis with pigmentary changes. She was then treated as a case of Pityriasis lichenoides chronica with topical, oral corticosteroids and topical 8-methoxypsoralen for three months which lead to remission of lesions for about one year. Two years after the first biopsy, she developed multiple asymptomatic ill-defined hypopigmented macules and patches over both the arms, thighs and left cheek, for which the second biopsy was done.

On histopathological examination, focal loss of basal cells and interface lymphocytic infiltration with intra-spinous lymphocytes and moderate perivascular lymphocytic infiltrate in superficial dermis were observed, reported as features suggestive of lupus erythematosus. ANA and dsDNA were negative. She was then treated with topical steroids with no improvement of the lesions. There was increase in hypopigmented macules over bilateral arms, forearms, bilateral thighs and few new erythematous papules over the previous hypopigmented patches in the abdomen (Figure 1,2,3 & 4) for which the third biopsy was sent, seven months after the second biopsy. The biopsy showed the presence of epidermotropic, predominantly CD4+ T-cell infiltration, epidermis with focal vacuolar interface dermatitis and exocytosis of small and slightly enlarged lymphocytes with cerebriform nuclei (Figure 5,6 & 7), and increased CD4:CD8 ratio in the epidermis as demonstrated in immunohistochemistry which were consistent with MF.

Blood workup and contrast-enhanced computed tomography scans of the neck, chest, and abdomen were performed for staging of disease, along with a hemato-oncologist consultation, all of which were unremarkable. The patient has been managed with topical corticosteroids and narrow-band UVB therapy for the past three months, with significant clinical improvement.

Discussion

Mycosis fungoides is a type of primary cutaneous T-cell lymphoma. It often causes significant challenges in diagnosis, especially at the early stage.[3] This condition frequently resembles benign skin disorders such as eczema, psoriasis, vitiligo, or pityriasis lichenoides chronica.[2] This is especially true when it appears as hypopigmented lesions in individuals with darker skin tones. These similarities can lead to misdiagnoses and delays in starting proper treatment, which can worsen the patient's condition. Specifically, hypopigmented MF is a rare variant that mostly affects children and young adults of Asian or African descent.[6] It usually presents as asymptomatic hypopigmented patches with slight scaling.

Diagnosing mycosis fungoides is challenging as the histopathological features are often unclear in the early stages. Initial biopsies may show nonspecific changes, such as slight spongiosis or perivascular lymphocytic infiltrates without any atypical cells. This means that multiple biopsies from different areas may be warranted to reach the correct diagnosis as in our case. Research on diagnostic delays indicates that the first biopsy only provides clear evidence in about 25% of

cases.[4] As the disease advances, the histopathology becomes more evident, showing atypical lymphocytes that migrate to the epidermis, Pautrier microabscesses, and band-like lymphocytic infiltrates in the superficial dermis.

Immunohistochemical analysis plays a vital role in confirming the diagnosis of MF. In most cases, MF is characterized by a predominance of CD4+ T-cells, leading to a higher CD4:CD8 ratio.[7] While our case demonstrated a classic CD4+ predominant phenotype, it is important to note that the hypopigmented variant can often exhibit a CD8+ cytotoxic T-cell phenotype, particularly in younger patients, which may be linked to a slower disease progression.[6] The diagnosis can be strengthened by using additional immunohistochemical markers, such as the loss of pan–T-cell antigens. Still, it is important to understand that no single marker can confirm the diagnosis. Therefore, a thorough and integrated diagnostic approach is necessary.

To improve diagnostic accuracy, molecular techniques such as T-cell receptor gene rearrangement analysis through polymerase chain reaction or next-generation sequencing can be used. Identifying a clonal T-cell population can help support an MF diagnosis when histological findings are unclear.

Diagnosing MF, especially the hypopigmented variant, requires strong suspicion from clinicians. They need to recognize its various forms that mimic other conditions and understand the importance of repeated clinical and histological assessments. A combined approach that includes clinical evaluation, serial skin biopsies, histopathology, immunohistochemistry, and molecular diagnostics is vital for achieving an early and accurate diagnosis.[8] Timely identification of this uncommon condition can lead to appropriate treatment, reduce disease burden, and improve long-term patient outcomes.

Conclusion

Hypopigmented MF is a variant of cutaneous T-cell lymphoma, and few cases are described in the literature. Since it can simulate other dermatologic disorders such as Hansen's disease, post–kala-azar dermal leishmaniasis, vitiligo vulgaris, a vigilant clinician should bear the possibility of cutaneous malignancies in mind. With the knowledge of this infrequent presentation especially among opportunistic infections, dermatologists who practice in low-resource settings can suspect, diagnose and make appropriate referrals to accessible services like histopathology including immunohistochemistry for early diagnosis and avoid associated morbidities with late presentation.

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