ISSN: 1307-7635

# TURKISH JOURNAL OF DERMATOLOGY

VOLUME 19 • ISSUE 1 • MARCH 2025

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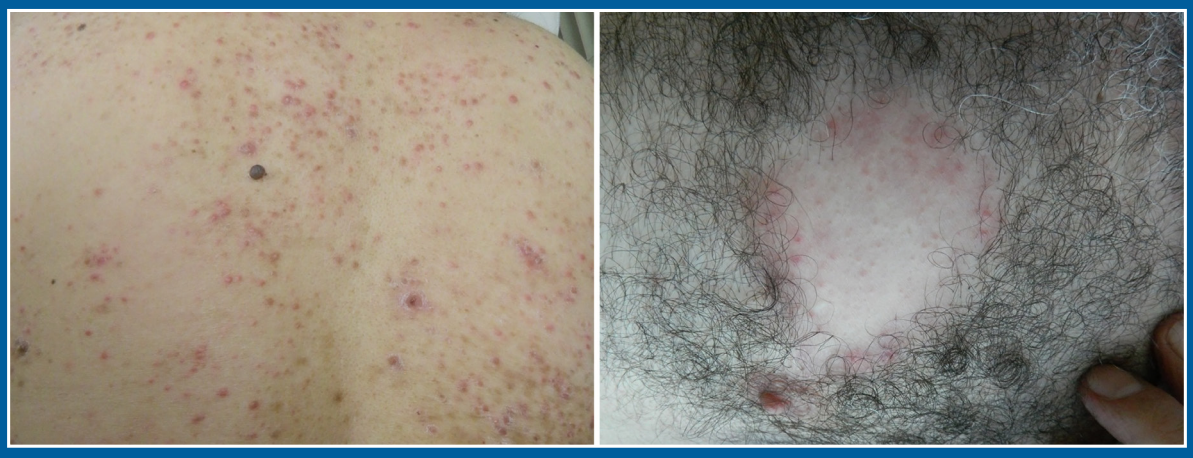

TURKISH SOCIETY OF DERMATOLOGY 1968

An Official Publication of Turkish Society of Dermatology

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**Owner:** Ertan Yılmaz on behalf of the Turkish Dermatology Society

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**Web:** www.galenos.com.tr **Publisher Certificate Number:** 14521

**Printing Date:** March 2025
**E-ISSN:** 1307-7635
International scientific journal published quarterly.

TURKISH
JOURNAL OF DERMATOLOGY

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Review

# Etiopathogenesis of Mycosis Fungoides

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## Abstract

Mycosis fungoides (MF), first described by Jean Louis Alibert in 1806, is the most common subtype of primary cutaneous T-cell lymphomas. MF is a subtype of non-Hodgkin lymphoma and is characterized by malignant clonal T-lymphocytes infiltrating the skin. Although MF primarily affects the skin in the early stages, it can also involve the lymph nodes, blood, and internal organs in more advanced stages. Although the exact cause of MF remains unknown, research suggests that genetic, immunological, environmental factors, and microbial agents may play a role in its pathogenesis. The most widely accepted theory assumes that clonal T-cells arise as a result of antigenic stimulation in genetically predisposed individuals, suggesting that chronic inflammation is crucial to disease development. In this review, we discuss the current knowledge of the factors contributing to the pathogenesis of MF. We collected data from PubMed searches using the combined terms "cutaneous T-cell lymphoma, mycosis fungoides, pathogenesis, etiology, etiopathogenesis" and applying the filters "Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review" without any date restriction.

**Keywords:** Cutaneous T-cell lymphoma, mycosis fungoides, pathogenesis, etiology, etiopathogenesis

## Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), primarily affecting the skin but capable of advancing to involve lymph nodes, blood, and other internal organs in later stages. MF is characterized by a clonal expansion of epidermal T-lymphocytes, resulting in distinctive cutaneous manifestations that vary from patches and plaques to tumoral growths. This pathological progression highlights the disease's complexity and indicates that genetic, environmental, immunological, and infectious factors may play a role in its development.[1]

Recent studies indicate that continuous antigenic stimulation in genetically predisposed individuals may initiate the clonal proliferation of T-cells, suggesting a potential connection between persistent inflammation and the pathogenesis of MF. Genetic research has identified numerous mutations and chromosomal anomalies, especially in genes that regulate the cell cycle, provide resistance to apoptosis, and modulate immunological checkpoints, all of which are essential to the course of MF.[2,3] Moreover, the impact of environmental and lifestyle factors, including occupational exposure and chronic antigenic stimulation, is under examination, with possible associations to particular industries and lifestyle practices, such as smoking and obesity.[4-7] Infectious agents, such as specific bacteria and viruses, have been investigated as potential catalysts for MF. While precise links to specific infections remain unclear, recent studies indicate that the skin-resident microbiota may affect disease progression and symptom severity.[8,9] Immunological variables significantly influence MF, with current research emphasizing the involvement of cytokine and chemokine signaling pathways in guiding the migration and behavior of malignant T-cells in the skin.[10-12]

This review aims to elucidate the present understanding of MF pathogenesis, highlighting the contributions of genetic, environmental, immunological, and microbiological components to disease initiation and progression.

**Submission:** 01-Oct-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 19-Oct-2024

Access this article online

Quick Response Code:

Website: www.turkjdermatol.com

DOI: 10.4274/tjd.galenos.2024.42714

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**How to cite this article:** Erdemir VA, Erdem O. Etiopathogenesis of mycosis fungoides. Turk J Dermatol. 2025;19(1):1-6.

## Genetic Factors

Understanding the genetic risk factors of MF is essential for early diagnosis, development of targeted therapies, and improvement of disease prognosis. Numerous genetic alterations and mechanisms potentially involved in the onset and progression of MF have been identified. Various genes involved in cell proliferation, immune checkpoint regulation, apoptosis resistance, and immune response are implicated in MF progression. Specific pathways, including those involved in cell cycle regulation, chromosomal instability, and DNA repair, are activated in MF.[2,3]

Familial clustering of MF suggests a genetic predisposition, with certain HLA class II alleles (e.g., *DRB111* and *DQB1*03) being more common in patients with both sporadic and familial MF. Additionally, it has been documented in multiple families, often involving first-degree relatives such as siblings or parent-child pairs. The clinical features and response to therapy are generally similar between familial and sporadic cases. However, some unique variants like hypopigmented MF, have been observed in familial cases.[13,14]

Conventional karyotypic studies have primarily focused on the blood of patients with Sézary syndrome because of the challenges of culturing tumor cells from MF skin lesions. However, these studies revealed multiple structural and numerical chromosomal abnormalities. The most frequently observed abnormalities include the loss of chromosomes 1, 10, and 17 and the gain of chromosome 7.[3,15] In addition, deletions in the 9p21 region, encompassing the *P15* and *P16* genes, are prevalent in both early and advanced phases of MF.[16,17]

Mutations in the *P53* gene are among the most frequent genetic anomalies in human malignancies. Mutations in the tumor suppressor gene *TP53* have been identified in approximately 40% of patients with tumor-stage MF.[18] Interestingly, the mutation spectrum aligns with ultraviyole B-induced mutations, suggesting that ultraviolet radiation may play a role in advanced cutaneous lymphomas.[15,18]

Frequent deletions of tumor suppressor genes, including *BCL7A*, *SMAC/DIABLO*, and *RHOF*, have been observed in early-stage MF, indicating their role in the initial pathogenesis of MF.[19] The loss of other tumor suppressor genes, such as *RB1* and *DLEU1*, has been associated with poor prognosis.[16] Additionally, the deletion of tumor suppressor genes including *CDKN2A* and *CDKN2B*, elevated expression of *NAV3*, *JUNB*, and *c-MYC*, and hypermethylation of mismatch repair genes have been documented.[20]

Some patients with MF harbor Fas mutations, which result in defective apoptosis and lead to the accumulation of malignant T-cells in the skin.[21]

Studies have also indicated the involvement of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway in MF pathogenesis and progression. Mutations in JAK3 have been identified in approximately 8.3% of patients with tumor-stage MF, and recurrent deletions of JAK-STAT pathway inhibitors, such as HNRNPK and SOCS1, have been observed. In the early stages of CTCL, STAT5 activation is prevalent, whereas STAT3 activation becomes predominant in the later stages.[3,22]

In the initial phases, interleukin-2 (IL-2), IL-7, and IL-15 induce STAT5 activation through JAK1 and JAK3 kinases, whereas in subsequent phases, autocrine stimulation by IL-21 is considered essential for STAT3 activation. Recent studies have provided molecular evidence indicating that overexpression of STAT5 during the initial stages of the disease results in elevation of oncogenic miR-155, which subsequently targets STAT4 mRNA. The absence of STAT4 signaling results in a transition from the Th1 phenotype to the Th2 phenotype in malignant T-cells. In advanced phases, STAT3 and STAT5 activation may become independent of cytokines and solely mediated by constitutively active JAK1 and JAK3 kinases.[23]

STAT3 activation plays a particularly important role in advanced-stage disease and large-cell transformation. Given these functions of the JAK-STAT pathway, JAK inhibitors have emerged as promising therapeutic targets for the treatment of MF.[24]

Studies have also demonstrated the activation of the nuclear factor-kappa B (NF-κB) pathway, which is critical for tumor resistance to apoptosis in CTCL. Genetic alterations in the NF-κB pathway genes *PLCG1*, *CARD11*, *TNFRSF1B*, and *KIT* have been reported. These alterations influence the regulation of T-cell survival, proliferation, and transcriptional programs following T-cell receptor signaling.[25]

PIM2, an oncogene regulated by pathways such as JAK-STAT and NF-B, has been implicated in CTCL pathogenesis. A previous study identified increased PIM2 expression in patients with MF, suggesting that it could serve as a marker to distinguish MF from benign inflammatory diseases.[26]

In recent years, there has been a growing interest in studying non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long ncRNAs, in the epigenetic regulation of CTCLs. These ncRNAs are crucial for modulating gene expression and are important for diagnosis, prognosis, and therapeutic decision-making. They play roles in tumor progression and modulating the tumor microenvironment, making ncRNA-based therapies a promising area of research for CTCL patients.[27]

## Environmental Factors

The increasing incidence of MF in recent years has prompted investigations into various environmental and lifestyle factors that may contribute to disease development. Persistent exogenous antigenic stimulation of Th-cells in the skin is a key factor in the clonal evolution of these cells.[28]

Although initial studies did not find a significant association between occupational exposure and the disease, later studies have yielded some notable findings.[29] In a study that collected data from Europe, North America, and Australia, an increased risk was identified among workers involved in vegetable and crop farming, as well as those involved in painting, carpet-making, and woodworking. However, this study did not examine the specific substances to which these workers were exposed in their occupations.[4] In a case-control study conducted in Europe, aromatic and/or halogenated hydrocarbons used as solvents and pesticides were identified as potential risk factors for MF.[5] Other industries found associated with an increased risk of MF include textile, petrochemical, and metalworking industries.[6]

Although studies on lifestyle factors have reported varying results regarding smoking, an increased likelihood of developing MF has been noted in individuals who have smoked for 40 years or more.[29] Obesity is one of the factors that stimulate inflammation.[7] One study found that a high body mass index [(BMI) $\geq$ 30 kg/m$^2$] increases the risk of developing MF, whereas increased physical activity was associated with a decreased risk.[29] Another lifestyle factor, heavy alcohol consumption ($\geq$ 24 g/day), is also linked to an increased risk of developing MF.[30]

There is no definitive evidence that drugs cause MF; however, certain medications, such as mogamulizumab, quinine, phenytoin, and carbamazepine, can induce reactions that mimic MF both clinically and histopathologically.[31,32]

Additionally, a family history of multiple myeloma and personal eczema for more than 10 years are considered risk factors for MF.[29]

## Infectious Factors

It is well established that certain bacteria and viruses are associated with human cancers, but the mechanisms by which cancers develop through these infections remain incompletely understood.

Studies on human T-lymphotropic viruses I and II and Epstein-Barr virus, which are linked to certain types of lymphomas, have found that these viruses do not play a role in the etiology of MF.[33,34] However, cytomegalovirus infection seropositivity has been detected in patients with late-stage MF patients.[35]

Studies on human herpesvirus 8 infection have also not found an association with MF, but a significant relationship has been identified with large plaque parapsoriasis.[36]

There are only a few studies regarding the role of the newly identified parvovirus cutavirus (CuV) in the etiology of MF. One of these studies specifically compared patients with large plaque parapsoriasis (BPP), which is considered a premalignant stage of MF, with those with inflammatory skin diseases.[37] Another study found that viral DNA was detected in the lesional skin of patients with BPP at a significantly higher rate (38%) than in those with inflammatory diseases.[38] Further research is needed to fully understand the impact of CuV infection on MF progression.

In a genetic study in which PCR was performed on skin biopsies, CuV DNA was not detected in patients with normal skin or skin carcinoma, but was found in 4 out of 17 patients with CTCL.

In a study conducted with the hypothesis that bacterial superantigen may lead to clonality by causing inflammation, *Staphylococcus aureus* was found in the blood and skin cultures of 75% of patients with advanced-stage disease and Sézary syndrome. In 50% of these cases, the bacteria produced enterotoxins, which act as superantigen, potentially leading to lymphoproliferative infiltrations.[39]

Additionally, a case-control study conducted in a region where Lyme disease is endemic detected *Borrelia burgdorferi*-specific sequences in 18% of patients with MF; however, this finding is not sufficient to conclude a definitive role for *Borrelia* in the etiology of MF.[40]

Recent research has also investigated the role of the skin microbiome in the pathogenesis and symptomatology of MF, aiming to understand how microbial communities influence the disease course and patient outcomes. Changes in the skin microbiota are associated with the severity of MF symptoms. Greater erythema has been associated with higher *Staphylococcus* levels, while discomfort and thicker skin have been linked to reduced levels of *Propionibacterium*.[8,9] *Staphylococcus aureus,* in particular, may contribute to the morbidity and development of MF. Furthermore, the integrity of the skin barrier and interactions between the host and microbiota are also linked to the disease advancement.[41]

## Immunological Factors

The immune milieu is essential for the progression of MF. In typical circumstances, T-cells that have not yet encountered their specific antigens continuously traverse from the bloodstream to lymph nodes to examine antigen-presenting cells that deliver peptides compatible with their

T-cell receptors. This process is predominantly mediated by cell surface markers, including L-selectin (CD62L) and CC chemokine receptor 7 (CCR7), present on naïve T-cells. Upon T-cell activation, alterations in the cell surface profile occur. The production of molecules including cutaneous lymphocyte antigen (CLA) and CCR4, which significantly enhance T cell migration to the skin, is induced in skin-draining lymph nodes.[10,11]

One of the primary responses of keratinocytes to cell damage and stress is the secretion of cytokines, which initiate and sustain cutaneous inflammation and promote leukocyte recruitment. This cytokine response stimulates the upregulation of adhesion molecules in dermal endothelial cells and the release of chemokines from basal keratinocytes. The movement of T cells along the sticky endothelium, utilizing a "tethering and rolling" technique, occurs through the interaction of CLA on T-cells with E-selectin on the endothelium. The lymphocytes then tightly adhere to the endothelium and extravasate into the dermis.[10]

In addition to the crucial role of CLA in the migration into the dermis, chemokines are considered to be responsible for epidermotropism.[42] The sources of chemokines are keratinocytes, Langerhans cells, and dermal fibroblasts.[43] In the early stages of MF, interactions between CXCL9, CXCL10, and CXCR3 appear to play key roles in the aggregation of tumor cells, whereas in the tumor stage of the disease, increased expression of CCR4 and decreased expression of CXCL9 and CXCL10 have been observed.[44] In the later stages, chemokine receptors like CCR7, which facilitate homing to the lymphatics, become dominant. Consistent with this, a previous study found a correlation between CCR7 expression and the subcutaneous spread of MF cells.[12]

Dendritic cells not only contribute to chemokine production during pathogenesis and should also be discussed within the context of the antigen hypothesis. Although their exact function is not fully understood, their presence in Pautrier microabscesses and a study showing that Sézary cells can survive long-term in cell cultures through stimulation by immature dendritic cells seem significant. Despite these findings, it should not be forgotten that dendritic cells are also crucial for immunity.[45,46]

Cytokines also play an important role in the pathogenesis of MF. Both Th1 (interferon-gamma, IL-2) and Th2 cytokines (IL-4, IL-5, IL-10) are important cytokines for MF. Different cytokines are associated with different disease stages. For instance, although Th1 and Th2 cytokine mRNAs are detected in the plaque stage, it has been reported that only Th2 cytokine mRNAs are detected as the disease progresses to the tumor stage.[47] The Th1 response is responsible for the eczema-like appearance in the early stages, whereas the Th2 response has been found to be associated with tumoral lesions and weakened immunity.[48,49]

## Conclusion

The pathogenesis of MF is a complex, multifactorial process influenced by genetic, immunological, microbiological, and environmental factors. Although significant progress has been made in understanding the roles of cytokines, chemokines, and immune cells such as T-cells and dendritic cells, the precise mechanisms that drive the initiation and progression of the disease remain incompletely understood. Continued research on these molecular and cellular interactions is crucial for improving diagnostic strategies and developing targeted therapies for MF, ultimately aiming to enhance patient outcomes.

### Footnotes

### Authorship Contributions

Concept: V.A.E., O.E., Design: V.A.E., O.E., Data Collection or Processing: V.A.E., O.E., Analysis or Interpretation: V.A.E., O.E., Literature Search: V.A.E., O.E., Writing: V.A.E., O.E.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Review

# Mycosis Fungoides: A Review of Clinical Findings

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## Abstract

Mycosis fungoides (MF) is defined as an epidermotropic primary cutaneous T-cell lymphomas characterized by T-helper phenotype T-lymphocytes with small to medium-sized cerebriform nuclei (though cytotoxic variants are not uncommon). MF is limited to the skin and can exhibit extracutaneous spread (lymph nodes, visceral organs) in advanced stages. The 2018 World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification recognizes the classical Alibert-Bazin MF type, as well as folliculotropic mycosis fungoides, pagetoid reticulosis, and granulomatous slack skin MF subtypes, which were first included in the 2005 WHO-EORTC classification. In addition to classical MF and its three variants, other clinicopathologic subtypes of MF have been described, including hypopigmented, poikilodermatous, erythrodermic, granulomatous, hyperpigmented, ichthyosiform, syringotropic, papular, purpuric, interstitial, pustular, bullous, verrucous, and psoriasiform MF. These subtypes exhibit clinical features similar to the diseases they mimic. It is essential to recognize the clinical features of both classical and variant forms of MF for early diagnosis and to consider the possibility of MF in the differential diagnosis. Dermatologists need to increase their awareness regarding this topic. This review discusses the clinical findings and variants of MF and highlights the key points of the diagnosis and treatment process.

**Keywords:** Mycosis fungoides, classic type, variants clinical findings

## Introduction

Primary cutaneous lymphomas are a heterogeneous group of extranodal (non-Hodgkin) lymphomas that originate from T- or B-lymphocytes, initially presenting with skin manifestations without evidence of extracutaneous involvement at diagnosis.[1] Cutaneous T-cell lymphomas (CTCL) constitute approximately 75-80% of all primary cutaneous lymphomas. Within this group, mycosis fungoides (MF) and Sézary syndrome (SS) are the most common malignancies. MF accounts for approximately 60% of CTCL and about 50% of all primary cutaneous lymphomas.[1-3]

MF is defined as an epidermotropic primary CTCL characterized by T-helper phenotype T-lymphocytes with small to medium-sized cerebriform nuclei (though cytotoxic variants are not uncommon). MF is limited to the skin and can exhibit extracutaneous spread (lymph nodes, visceral organs) in advanced stages. Bone marrow involvement is rare, and it follows an indolent clinical course.[4] This term is reserved for the classical clinical presentation characterized by patch, plaque, and tumor development, or for variants with a similar clinical course.[5]

The incidence of MF is 6-7 per million individuals, with a higher prevalence in black individuals.[6] The disease typically affects individuals between 55 and 60 years of age,[7] and its incidence increases with age, peaking after 70 years. Diagnosis occurs at a younger age in black individuals (median age at diagnosis is 53 years in blacks and 63 years in whites), and survival rates are lower in black patients, regardless of age and clinical stage.[8] The disease can also occur in children and adolescents, where it is the most common type of cutaneous lymphoma.[8] MF is more common in men, with a male-to-female ratio of 1.6 to 2:1.[2,7]

**Submission:** 17-Oct-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 14-Nov-2024

Access this article online

Quick Response Code:

**Website:** www.turkjdermatol.com

**DOI:** 10.4274/tjd.galenos.2024.66375

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**How to cite this article:** Küçük ÖS. Mycosis fungoides: a review of clinical findings. Turk J Dermatol. 2025;19(1):7-18.

The etiopathogenesis of cutaneous lymphomas is not fully understood. Chronic activation of T-cells by antigen-presenting cells is believed to gradually lead to the accumulation of mutations that promote the development of neoplastic cells.[9] However, the exact trigger for this chronic stimulation remains unclear, and the condition is thought to be multifactorial, with possible triggers varying among patients. Potential causative factors include genetic dysregulation, bacterial, viral, fungal, and mycobacterial infections, ultraviolet light exposure, and chemical exposure (environmental or occupational). Hydrochlorothiazide diuretics, immunosuppression, air pollution, and exposure to pesticides and detergents may increase the risk of developing MF, SS, and other non-Hodgkin lymphomas. Various infectious agents have been suggested as triggering and promoting agents, including *Staphylococcus aureus (S. aureus)*, dermatophytes, *Mycobacterium leprae*, *Chlamydia pneumoniae*, human T-cell lymphotropic virus type 1, Epstein-Barr virus, and herpes simplex virus.[9] *S. aureus* has been shown to activate oncogenic STAT3 signaling in malignant T-cells and upregulate interleukin-17 (IL-17) expression. Staphylococcal enterotoxin A type indirectly affects malignant T-cells by activating non-malignant T-cells, which produce IL-2 and other regulatory cytokines in response to this stimulus. These cytokines stimulate nearby malignant T-cells to upregulate JAK3/STAT3 and STAT5 signaling, leading to IL-17 upregulation. Aberrant expression of cytokine signaling 3 (SOCS3), a JAK3/STAT regulator, disrupts the normal expression of several cytokines, including IL-5, IL-10, IL-17A, and IL-17F.[9,10] It has been shown that the expression of tumor suppressor microRNA (miR)-22 is low in malignant T-cells and that this low expression occurs because of the binding of STAT5 to the promoter region of this gene.[9] The Th-2 immune-mediated response is accelerated by downregulation of STAT4 and upregulation of STAT5 and STAT3 by oncomiRs (miR-155) making CTCL patients more susceptible to *S. aureus* colonization and prolonged antigenic stimulation.[10]

Advances in technology, such as next-generation high-throughput sequencing (NGS), have enabled a better understanding of the genetic and epigenetic changes in CTCL. In genome sequencing studies of patients with MF, p53 mutations are observed, especially in the tumoral stage. Loss-of-function mutations in *ZEB1*, *ARID1A*, *CDKN2A*, *CDKN2B*, and *RB1* genes and mutations causing the activation of oncogenes such as *JUNB*, *PLCG1*, and *MYC* have been frequently reported. Overexpression of the cell cycle genes *CCND1*, *CCDN2*, and *CCDN3* has also been observed in MF lesions.[11] In addition to previously reported MF-associated mutations such as *DNMT3A*, *STAT5B*, and *SOCS1*, novel mutations were detected in genes such as *HLA-DRB1*, *AK2*, *ITPKB*, *HLA-B*, *TYRO3*, and *CHD2* by NGS. The identified variants were involved in the apoptotic, NF-B, JAK-STAT, and TCR signaling pathways. NGS can enhance the diagnosis of MF. The detection of pathogenic variants known to be present in MF favors a neoplastic diagnosis over an inflammatory diagnosis.[12] The existence of familial MF cases and studies showing a relationship between various HLA alleles (HLA-Dalleles (ADRB1) and the risk of MF development also support the hypothesis that genetic factors may play a role in the development of the disease. Studies investigating the relationship between vitamin D levels, vitamin D receptor polymorphism, and MF have found that vitamin D deficiency is more common in patients with MF than in healthy controls.[9-11]

The 2018 World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification recognizes the classical Alibert-Bazin MF type, as well as folliculotropic mycosis fungoides (FMF), pagetoid reticulosis, and granulomatous slack skin MF subtypes, which were first included in the 2005 WHO-EORTC classification.[3] The WHO-EORTC classification of 2018 is shown in Table 1.[13] In addition to classical MF and its three variants, other clinicopathologic subtypes of MF have been described, including hypopigmented, poikilodermatous, erythrodermic, granulomatous, hyperpigmented, ichthyosiform, syringotropic, papular, purpuric, interstitial, pustular, bullous, verrucous, and psoriasiform MF. These types are included in the classical Alibert-Bazin MF group because of their similar prognostic characteristics.[14,15]

The time between the onset of symptoms and the diagnosis of MF varies between 2 and 4.2 years.[16-18] The Prospective Cutaneous Lymphoma International Prognostic Index study found a diagnostic delay in early-stage MF, with an average duration of 36 months between the first symptoms and diagnosis.[17] Cutaneous lymphomas are rare and often misdiagnosed as eczematous diseases, particularly in the early stages. Moreover, there is no gold standard test for diagnosing MF, and a combination of clinical, histopathological, and molecular findings is necessary, thereby contributing to diagnostic delays. This review discusses the clinical findings and variants of MF and highlights the key points of the diagnosis and treatment process.

## Classical Mycosis Fungoides

Classical MF, also known as the Alibert-Bazin type, is a slowly progressive disease. It is the most common type, accounting for 88.6% of cases.[3] It is characterized by patch, plaque, and tumor stages (Figure 1A-C).[2] The clinical course generally lasts for years. Most patients with MF (70%) have early-stage disease at the time of initial diagnosis (stage IA-IIA).[17] Progression occurs in 25% of patients with early MF.[18]

Patches are the clinical manifestations of early MF. In advanced disease, they may coexist with plaques and tumors. Relapses may also occur in patients with MF who are in remission.[5] Patches present as erythematous lesions that are variable in scaling (usually fine scaling), variable in size (typically larger than 5 cm), prefer sun-protected areas, and may be generalized or localized (often involving a few regions), flat, or atrophic. The atrophic lesions appear wrinkled, like cigarette paper. These lesions, which may be intensely itchy or asymptomatic, persist. They are resistant to topical corticosteroid treatment, or they recur after treatment is discontinued. Untreated lesions grow slowly, whereas irregular lesions may appear in spontaneously regressing areas. Patch lesions in women are particularly located on the hips and breasts. The lower trunk, inguinal and axillary areas, and proximal regions of the upper and lower extremities are frequently affected. In classical MF, lesions are usually multiple and can sometimes be widespread (Figure 2A, B). Not all patients with MF progress from patches to plaques and tumors; however, patches are always present.

Plaque lesions appear as irregular or elevated irregular, variably scaly, erythematous, or reddish-brown lesions. Patches may progress to well-demarcated, erythematous, infiltrated plaques with bizarre contours, foveolar, semi-annular, and serpiginous appearances. It is common to see patches, plaques, and tumors together. MF plaques must be differentiated from flat tumors. In patients with darker skin tones, MF patches and plaques are less erythematous and appear grayish or silver (Figure 3A, B).[5]

In the patch and plaque stages, MF can resemble many benign inflammatory dermatoses, such as chronic eczema, atopic dermatitis, nummular dermatitis, pityriasis rosea, pityriasis lichenoides chronica, psoriasis, tinea corporis, syphilis, and parapsoriasis.[19] The diseases most frequently included in the differential diagnosis of classic MF patch/plaque stages are presented in Table 2. In addition, MF occasionally occurs with or after inflammatory skin diseases, such as psoriasis and atopic eczema.[20] To avoid delay in the diagnosis of early-stage MF, multiple biopsies should be performed from different areas, and different lesions should be examined, and histopathological evaluation should be performed by experienced pathologists. Identification of a malignant clone is critical for early-stage MF. *T-cell receptor (TCR)* gene rearrangements have been detected by Southern blotting or polymerase chain reaction for this purpose; however, the results of these methods may be insufficient. NGS is more sensitive and specific than existing methods, making it useful for detecting early MF lesions and monitoring response to therapy. Furthermore, based on high-throughput DNA sequencing of the *TCRβ* gene, a tumor clone frequency of > 25% was found to be a strong predictor of disease progression and poor survival in patients with MF whose disease is limited to the skin.[20]

Tumors can be solitary, localized, or generalized. They may be observed in combination with typical patches and plaques or without other lesions. If tumors are present without patches, other cutaneous lymphomas should be considered in the differential diagnosis. Lesions tend to be multiple. A leonine

**Table 1. Current classification of skin lymphomas[13]**

| **WHO-EORTC classification (2018)** |
|---|
| **Cutaneous T-cell lymphomas** |
| • Mycosis fungoides (MF) |
| ◦ MF variants and subtypes: |
| ▪ Folliculotropic MF |
| ▪ Pagetoid reticulosis |
| ▪ Granulomatous slack skin |
| • Sézary syndrome |
| • Adult T-cell leukemia/lymphoma |
| • Primary cutaneous CD30+ lymphoproliferative disorders: |
| ◦ Primary cutaneous anaplastic large cell lymphoma |
| ◦ Lymphomatoid papulosis |
| • Subcutaneous panniculitis-like T-cell lymphoma |
| • Extranodal NK/T-cell lymphoma, nasal type |
| • Chronic active EBV infection* |
| • Primary cutaneous peripheral T-cell lymphoma, not otherwise specified** |
| ◦ Primary cutaneous γ/δ T-cell lymphoma** |
| ◦ Primary aggressive epidermotropic CD8+ T-cell lymphoma (provisionally valid) |
| ◦ Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder (provisionally valid)** |
| ◦ Primary cutaneous acral CD8+ T-cell lymphoma (provisionally valid)** |
| ◦ Primary cutaneous peripheral T-cell lymphoma, unclassified |
| **Cutaneous B-cell lymphomas** |
| • Primary cutaneous marginal zone lymphoma |
| • Primary cutaneous follicle center lymphoma |
| • Primary cutaneous diffuse large B-cell lymphoma, leg type |
| • EBV+ mucocutaneous ulcer (provisionally valid) |
| • Intravascular large B-cell lymphoma |

*New entity added to the WHO-EORTC 2018 classification,** Updated name in the WHO-EORTC 2018 classification, NK: Natural killer, EBV: Epstein-Barr virus

**Table 2. Differential diagnosis of classic MF patch/plaque stage**

| |
|---|
| Atopic dermatitis |
| Contact dermatitis |
| Nummular dermatitis |
| Psoriasis |
| Pityriasis rosea |
| Pityriasis lichenoides chronica |
| Tinea corporis |

MF: Mycosis fungoides

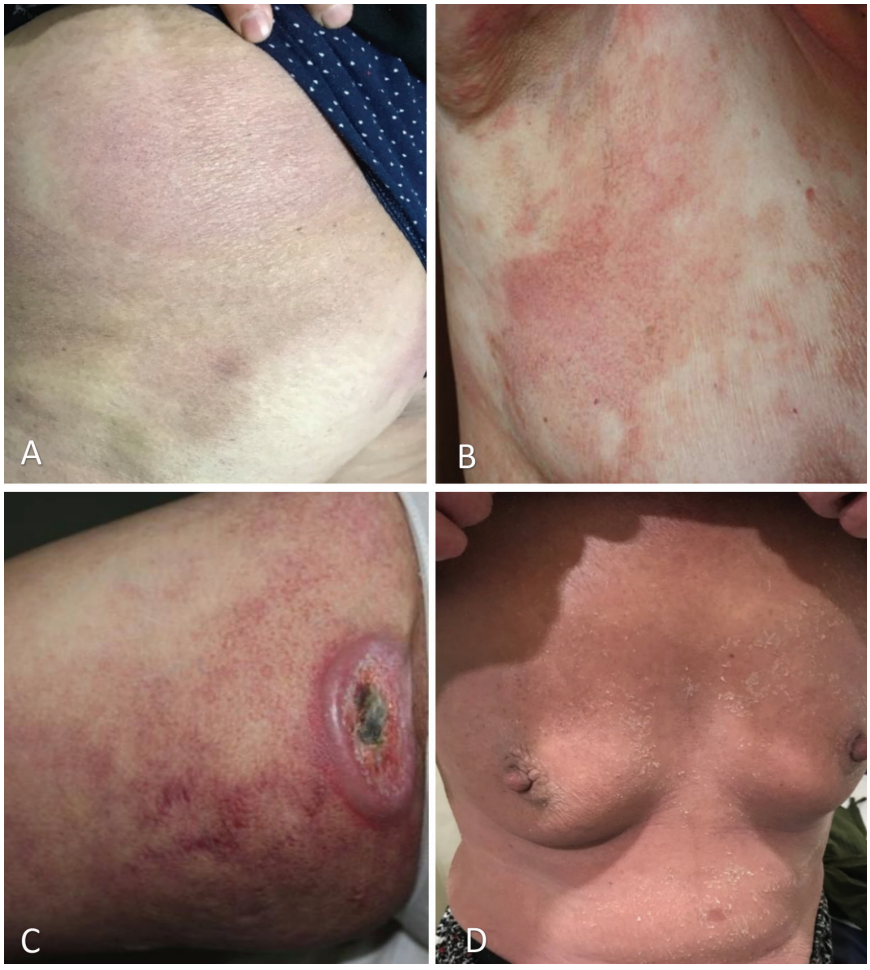


**Figure 1.** Clinical findings of classical mycosis fungoides: patch on the leg (A); plaques on the right lateral side of the body leg (B); tumor on the right inguinal area (C); and erythroderma (D)

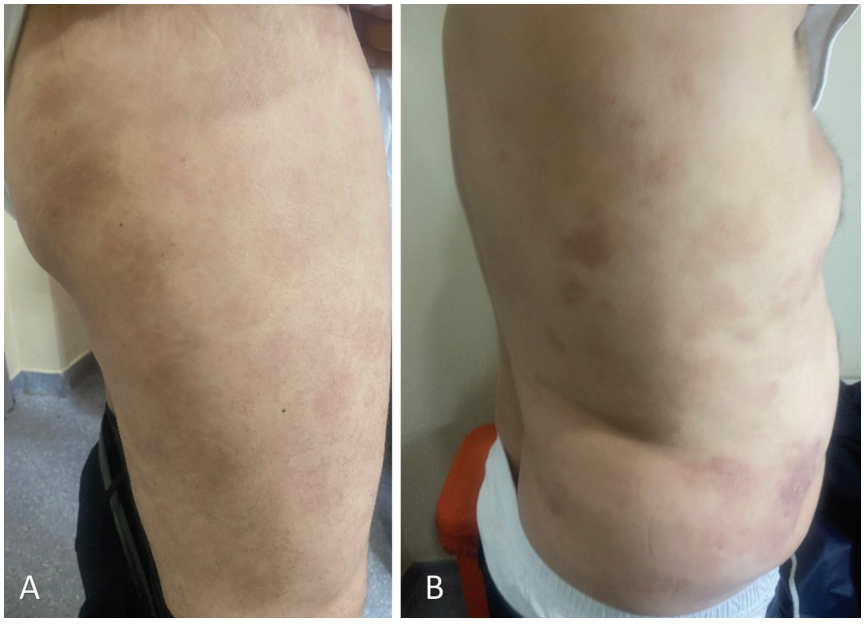


**Figure 2.** Clinical findings of classical mycosis fungoides: patches on the leg (A); patches and thin plaques on the trunk (B)

facies may develop when tumors are located on the face. Other commonly affected areas include the axillae, inguinal region, submammary region, and antecubital region (Figure 4). In this stage, mucosal lesions may also occur.[21] The growth rate of tumors in MF varies; they may grow rapidly within a few weeks or remain relatively stable for months. Partial regression may be observed. Itching may become severe. Thick plaques, especially tumors, often ulcerate, with necrosis and secondary infection possible.[22] More than 50% of MF-related deaths result from sepsis caused by *S. aureus* or *P. aeruginosa*.[23] Tumors may transform into a CD30+ (Ki-1+) large-cell anaplastic variant of CTCL, which occurs in 8-55% of cases.[24,25] Unlike primary CD30+ anaplastic large-cell lymphomas, which generally have a good prognosis, CD30+ lymphomas secondary to MF have a poor prognosis, with a median survival of 11-36 months after transformation.[23,25,26]

Erythroderma is defined as bright red erythema covering more than 80% of the body surface and accompanied by scaling. There is fever, chills, weight loss, and severe pruritus. Erythema, scaling, hyperkeratosis, and fissures are seen on the palms and soles. Lymphadenopathy is commonly observed. Alopecia, ectropion, and nail changes may also occur. When erythroderma develops in patients with MF, SS must be distinguished. While MF erythroderma and SS were historically considered part of the same CTCL group because of their similar histopathological features, they are now classified as separate entities in the WHO-EORTC classification.[2,3] They exhibit different molecular characteristics, have distinct prognoses, and require different management. In a study of 1,502 patients with MF/SS, 71.4% had patches, 36.3% had plaques, and 13.5% had tumors. Erythroderma is observed in 16.6% of cases.[27]

MF lesions typically first appear in sun-protected areas, particularly on the buttocks and breasts. The lower trunk, groin, axillae, and proximal areas of the upper and lower extremities are frequently affected. Lesions appear in variable numbers and gradually spread. All these features are included in the clinical criteria for early MF diagnosis proposed by Pimpinelli et al.[28] (Table 3).[29]

## Mycosis Fungoides Variants (Subtypes) in Current Classification

**Folliculotropic mycosis fungoides:** This subtype is the most common MF subtype, accounting for 11.4% of cases.[3] Follicular involvement leads to erythematous follicular papules and small cysts, acneiform/comedo-like papules or nodules,

**Table 3. Clinical features of the algorithm for early-stage MF diagnosis[28]**

| Main criteria | | |
|---|---|---|
| **Criteria** | **Major (2 points)** | **Minor (1 points)** |
| Clinical | Persistent/progressive | Main criterion + any two |
| Patch or thin plaques | | |
| | 1) Location in a sun-protected area | Main criterion + any one |
| | 2) Difference in shape and size | (1 point) |
| | 3) Poikiloderma | |

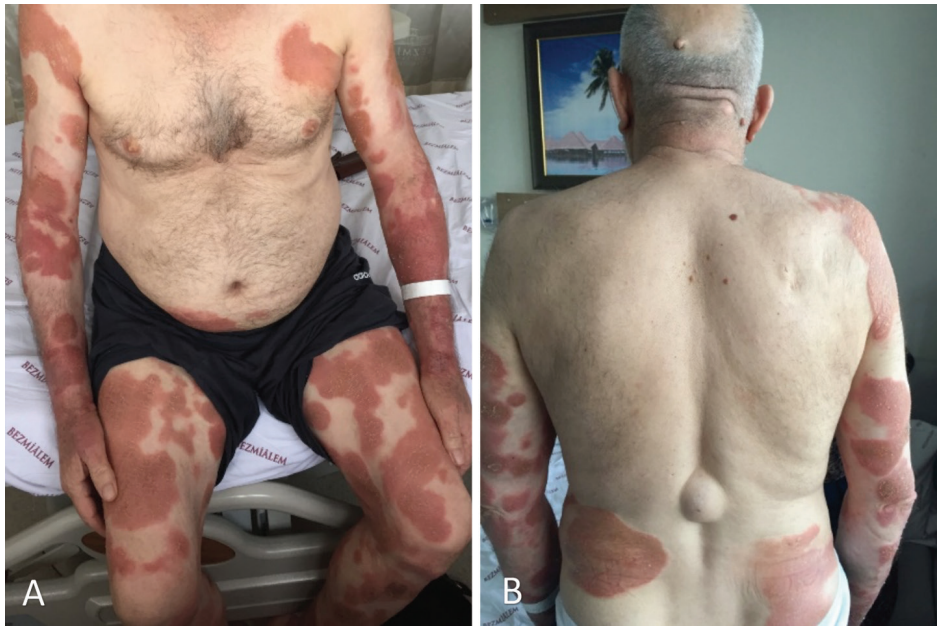


**Figure 3.** Clinical findings of classical mycosis fungoides: plaques on the anterior surface of the trunk and extremities (A); plaques on the posterior surface of the trunk, hips, and extremities (B)

indurated erythematous plaques, rosacea-like changes, and multiple milia. Lesions are often accompanied by alopecia, particularly affecting the eyebrows and scalp (Figure 5A, B). Infiltrated plaques with eyebrow hair loss are frequent and quite characteristic. Lesions are usually pruritic and are sometimes associated with burning sensations. Most patients are older men, but it also occurs in children and adolescents.[1,30] Due to the presence of deeper dermal neoplastic infiltrate, FMF is considered a variant with a worse prognosis. However, recent studies have classified FMF into two forms: an advanced form with infiltrated plaques and tumors located on the head and neck, accompanied by intense pruritus, scarring alopecia, and worse prognosis; and an early form with better prognosis, characterized by follicular accentuation, comedones, and milia on the trunk, with less pruritus.[31,32] Histologically, hair follicles are infiltrated by neoplastic cells, with or without mucin. The mucinous degeneration of hair follicles is called follicular mucinosis.[33]

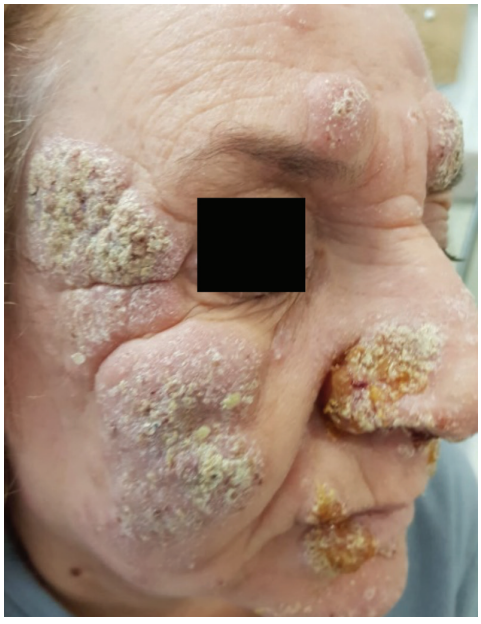

**Figure 4.** Clinical findings of classical mycosis fungoides: exophytic tumors on the face

**Pagetoid reticulosis (Woringer-Kolopp):** A rare and slowly progressive MF variant with a good prognosis. Typically, it presents as a solitary lesion localized to the acral areas of the extremities. The lesions are typically psoriasiform, hyperkeratotic, erythematous, or plaque (Figure 6). In the clinical differential diagnosis, solitary plaque psoriasis, Bowen's disease, superficial basal cell carcinoma, epilesional MF, and MF palmaris et plantaris must be considered. The slow, indolent course does not differentiate pagetoid reticulosis from these conditions, but the histopathological findings are pathognomonic. Histopathologically, there is a pagetoid proliferation of atypical T-lymphocytes with epidermal hyperplasia, which may be CD4+, CD8+, or CD4-CD8-.[22,34,35]

## Granulomatous Slack Skin

It is a rare and slow-progressing variant of MF with distinct clinical and histopathological features. Initially, erythematous infiltrative papules and plaques in the skin folds transform into loose, sagging skin folds over time. Typically localized in the flexural regions, especially the axilla and inguinal areas. It tends to occur in men between the third and fifth decades of life. The clinical course is generally slow. Histopathologically, granulomas, elastophagocytosis, and atypical lymphocytes infiltrating the skin are observed.[36,37] Patients with granulomatous slack skin have an increased

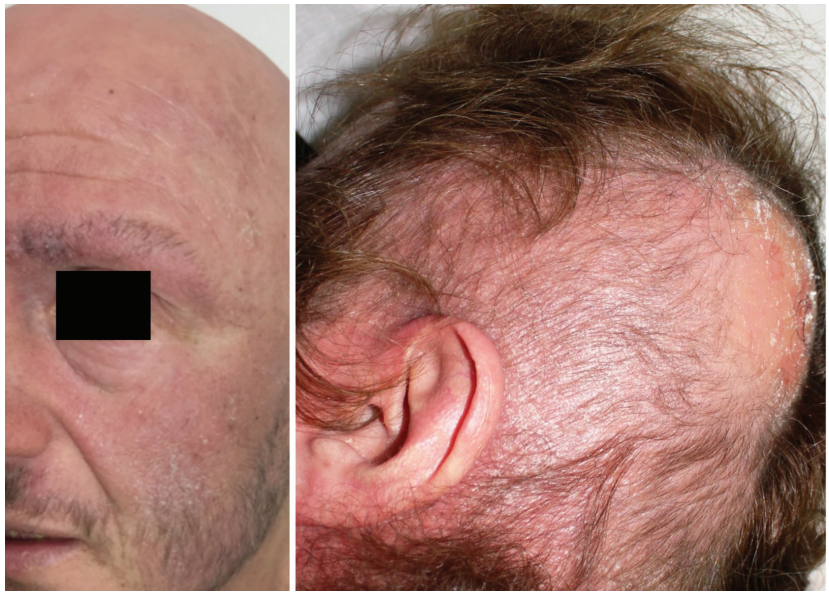

**Figure 5.** Clinical findings of folliculotropic mycosis fungoides: eyebrow alopecia (A); alopecic patch on the scalp (B)

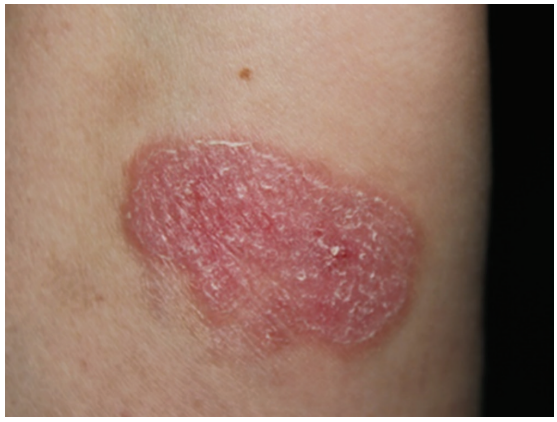

**Figure 6.** Pagetoid reticulosis (Woringer-Kolopp): erythematous-scale plaque lesion on the upper extremity

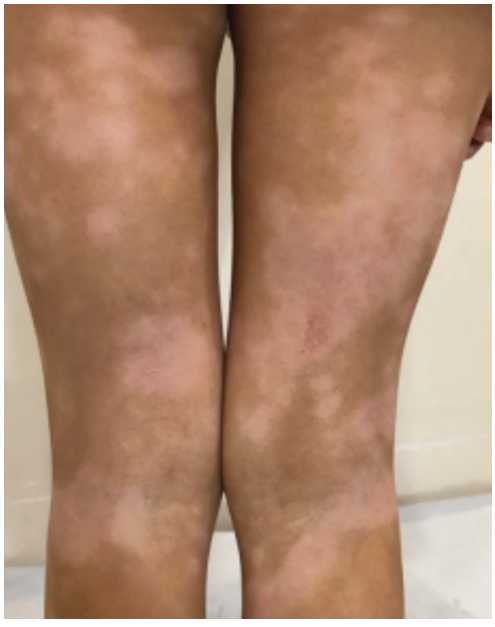

**Figure 7.** Clinical findings of hypopigmented mycosis fungoides: hypopigmented macules and patches on the lower extremities

risk of developing second hematological malignancies, particularly anaplastic large T-cell lymphoma and Hodgkin lymphoma.[37] Granulomatous mycosis fungoides (GMF) is differentiated from granulomatous slack skin by the presence of small sarcoidal granulomas dotted through the dermis and the absence of elastophagocytosis. Primarily, the distinction between granulomatous slack skin and granulomatous MF is made clinically.[7] Some authors suppose that the differences observed between GMF and GSS are one degree and secondary to their anatomic location rather than reflecting meaningful separate entities.[36,37] GMF is a rare form of MF (< 3% of cases) defined by a granulomatous reaction around the malignant lymphoid infiltrate. In contrast to classic MF, cutaneous lesions in GMF tend to involve distal extremities (lower legs, feet, hands) early in the disease course. It is reported in the literature that 30% of patients with GMF develop organ metastases, and the majority of metastases are detected in the lungs. In retrospective case-control studies, patients with GMF had poorer response to treatment, more secondary malignancies (SMs), increased progression to higher disease stages, and lower 5-year survival compared with those with classical MF.[38]

An increased risk of developing secondary hematological malignancies has been consistently observed in MF patients in the literature. Atci et al.[39] found SMs in 7.1% of 730 patients with MF. The most identified SMs were hematologic malignancies (64.3%), including lymphomatoid papulosis, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. The other most commonly associated malignancies were breast cancer, prostate cancer, renal cell carcinoma, melanoma, and Kaposi's sarcoma.[39]

## Other Mycosis Fungoides Subtypes

### Hypopigmented Mycosis Fungoides

Among the other MF subtypes included in the classical MF group, hypopigmented mycosis fungoides (HMF) is second in frequency (3% to 10%).[26,40] HMF is characterized by hypopigmented macules and patches without atrophy (Figure 7). HMF generally affects children and adolescents with darker skin types (Fitzpatrick types IV-VI). It is one of the most common variants observed in childhood (50%), but it has also been reported in adults. Lesions typically occur on the trunk, thighs, buttocks, and extremities.[26,41,42] Generally, HMF has an excellent prognostic outcome, and the immunohistochemical results are different from those of classic MF. It responds well to narrowband ultraviolet B phototherapy, especially in cases of juvenile onset. Hypopigmented lesions can sometimes be the sole finding of MF, although characteristic erythematous patches or plaque lesions are often observed. Patients generally have a non-specific clinical presentation.[42] The differential diagnoses include atopic dermatitis, pityriasis alba, leprosy, vitiligo, post-inflammatory hypopigmentation, pityriasis lichenoides chronica, pityriasis versicolor, syphilis, and idiopathic guttate hypomelanosis.[15] Although diagnostic delay is common in patients with HMF due to non-specific clinical features, the rate of disease progression is low, and the prognosis is good.[42]

Some cases of hypopigmented MF may have a CD8+ immunophenotype, as in cases of pagetoid reticulosis. Overall, only 5% of MF cases were CD8-positive. There are not enough data on CD8+ MF. A study noted the fact that CD8+ MF is not a single entity, but rather a "mixed-bag" of presentations, with some having more indolent courses similar to the typical CD4+ MF, such as those with hypopigmented patches often

found in the younger population, and others demonstrating a more aggressive course.[43] Other studies have concluded that CD8+ MF has an indolent course, and skin-directed treatments were effective in controlling the disease in most patients.[44] The correct diagnosis of CD8+ MF requires the exclusion of aggressive cytotoxic lymphomas, such as primary cutaneous aggressive epidermotropic T-cell lymphoma and dermal variants of CD8+ CTCL, as well as CD8+ pseudolymphomas in immunosuppressed CD4+ lymphopenic patients.[45]

## Poikilodermatous Mycosis Fungoides

Classically defined as poikiloderma vascular atrophicans, it is one of the most common variants (10-11%). It presents as plaques with telangiectasia, hypo/hyperpigmentation, and atrophy. The most affected areas were the breasts in women, and trunk, buttocks, and flexural areas in both men and women (Figure 8A-C). It is more frequently observed in younger patients (median age at diagnosis is 40 to 50 years). The poikilodermatous MF can be classified into localized and generalized forms. In patients with generalized poikilodermatous MF, erythroderma is seen (affecting more than 80% of the body surface area). Despite widespread skin involvement, the prognosis is excellent, and the lesions respond well to phototherapy.[46]

## Hyperpigmented Mycosis Fungoides

A very rare variant characterized by hyperpigmented macules and plaques, which are more common in patients with darker skin tones. Hyperpigmented MF can occasionally be observed in conjunction with other rare variants, but the hyperpigmentation is not due to previous poikilodermic changes or residual hyperpigmentation. It is predominantly characterized by the CD8+ phenotype.[47] Histopathologically, in addition to the classical MF features, abundant melanin granules in keratinocytes and Langerhans cells, along with pigment incontinence and numerous melanophage in the papillary dermis, are observed. It has an indolent, relatively non-aggressive course.[15]

## Pigmented Purpuric Dermatosis-Like Mycosis Fungoides

Clinically presents as persistent and widespread pigmented purpuric dermatosis-like lesions (Figure 9A, B). Histologically, it is characterized by a band-like infiltrate of atypical lymphocytes along with extravasated erythrocytes and hemosiderin-laden macrophages. This variant is more common in men. The greatest diagnostic challenge lies in distinguishing MF from benign purpuric dermatoses, as these conditions overlap both clinically and histopathologically with purpuric MF.[15,37] Serial biopsies from atypical pigmented purpuric lesions are necessary for histopathological diagnosis.[48]

## Erythrodermic Mycosis Fungoides

Erythrodermic mycosis fungoides (EMF) is the erythrodermal form of MF with confirmed histopathological features. Erythroderma can progress from plaque or patch MF or occasionally appears *de novo*. Itching is usually significant and may rarely precede the onset of skin lesions. EMF can be confused with SS. Lymphadenopathy is less common in EMF than in SS, and the typical blood involvement seen in SS is generally absent in EMF.[46] Psoriasis, eczema, pityriasis rubra pilaris, drug eruptions, and SS must be ruled out.[15,49]

## Ichthyosiform Mycosis Fungoides

A rare variant of early MF, which is more common in young individuals, with a relatively good prognosis. The condition typically affects the lower extremities and is characterized by geographic plaques resembling the cobblestone pattern of ichthyosis vulgaris (Figure 10). Ichthyosiform MF may occur alone or in combination with classical MF lesions or other MF variants, particularly follicular papules and other

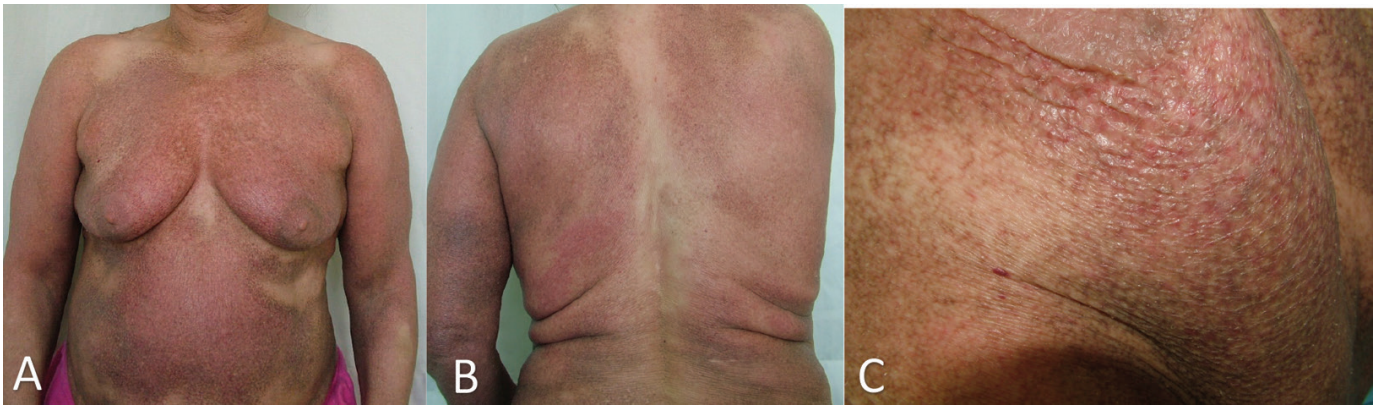


**Figure 8.** Clinical findings of poikilodermatosis mycosis fungoides: anterior trunk (A), posterior trunk (B), close-up view of poikiloderma (C)

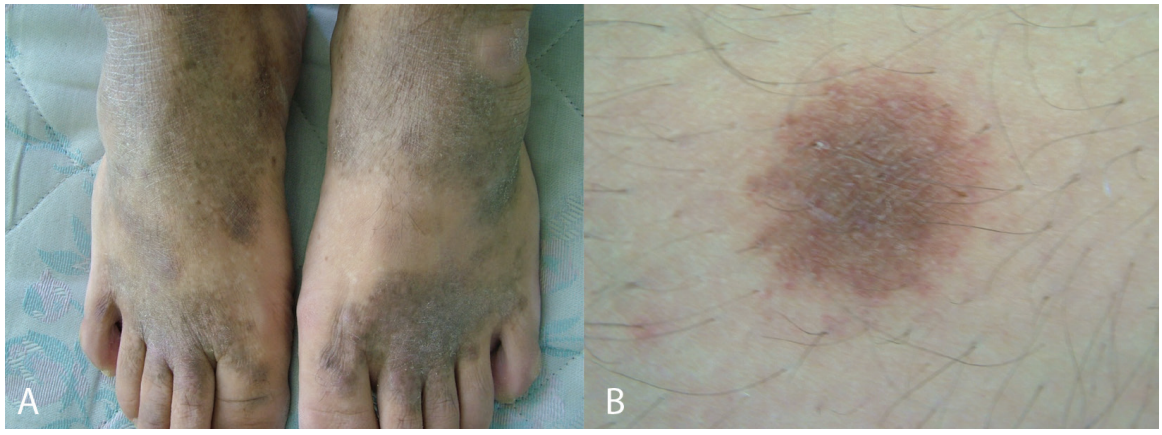


**Figure 9.** Clinical findings of pigmented purpuric dermatosis-like mycosis fungoides: bilateral lesions on the foot (A), close-up view of a single lesion (B)

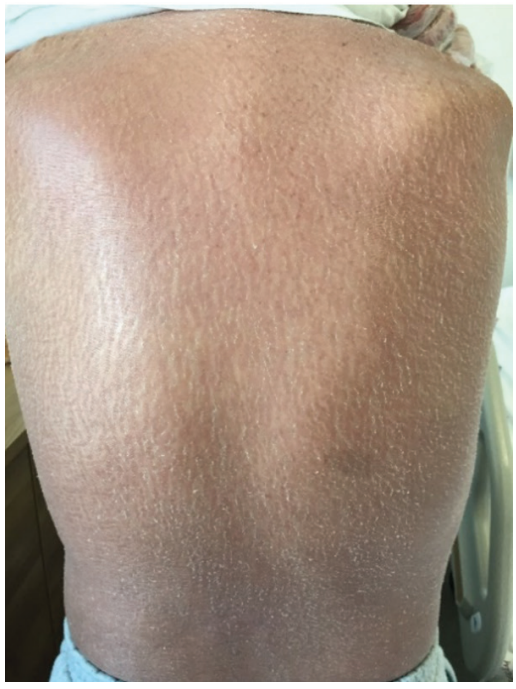

**Figure 10.** Clinical finding of ichthyosiform mycosis fungoides

characteristic lesions of FMF. The histopathological findings of classical MF are seen together with ichthyosis features, such as hypogranulosis and hyperkeratosis.[50]

## Acanthosis Nigricans-Like Mycosis Fungoides (Vegetative or Papillomatous Mycosis Fungoides)

Filamentous or vegetative MF lesions resemble acanthosis nigricans or seborrheic keratosis. They are usually localized to the neck, axilla, and inguinal folds (Figure 11). Histopathologically, marked acanthosis and papillomatosis are seen with a band-like infiltration of atypical lymphocytes, with or without epidermotropism.[15]

## Pustular Mycosis Fungoides

A very rare variant, later described by Ackerman as a long-standing vesicular-pustular eruption that eventually progresses to typical MF plaques. Pustules can be generalized or limited to the palmoplantar surface (Figure 12). Histopathologically, in addition to typical MF features like band-like atypical lymphocyte infiltration, epidermotropism, and Pautrier microabscesses, subcorneal pustules containing atypical lymphocytes, neutrophils, and eosinophils are observed. The ratio of neoplastic to inflammatory cells may vary, but neoplastic cells can become predominant over time.[15]

## Vesiculobullous Mycosis Fungoides

A rare clinicopathological variant characterized by vesiculobullous lesions. The lesions may be flaccid or tense and usually affect large areas of the chest and extremities. Surface erosion may occur following bullae rupture. It is more common in the elderly. Bullous lesions frequently accompany classic MF lesions and can either be the first sign of MF or appear later in the disease course. When bullae are limited to the palms and soles, dyshidrotic MF is used. The prognosis is poor. Histopathologically, vasiculobullous MF is characterized by spongiosis, intraepidermal or subepidermal blisters, and classic features of MF, such as atypical lymphocytes, epidermotropism, and Pautrier microabscesses.[15,51,52] Negative direct and indirect immunofluorescence results help distinguish this variant from autoimmune bullous diseases. Other causes of bullous lesions, such as drug and infection, should be considered in the differential diagnosis.[51] Many hypotheses regarding the mechanism of vesiculation have been proposed. The confluence of Pautrier's microabscesses in the MF may lead to bullae formation. The proliferation and accumulation of neoplastic lymphocytes in the epidermis may result in a loss of coherence between basal keratinocytes and the basal lamina, leading to the formation of vesicles.[52] Vesiculobullous

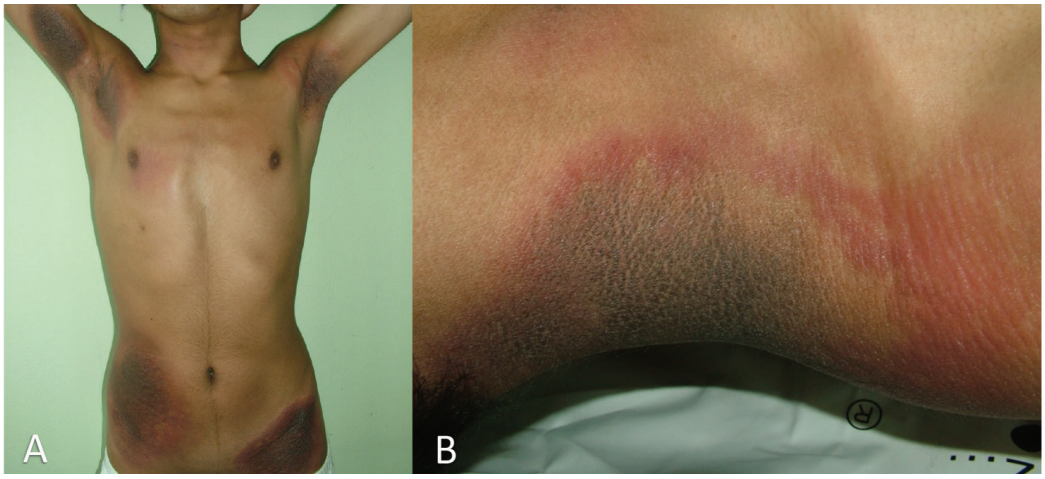


**Figure 11.** Clinical findings of papillomatous mycosis fungoides: anterior surface of the trunk (A) with an acanthosis nigricans-like lesion in the axillary region

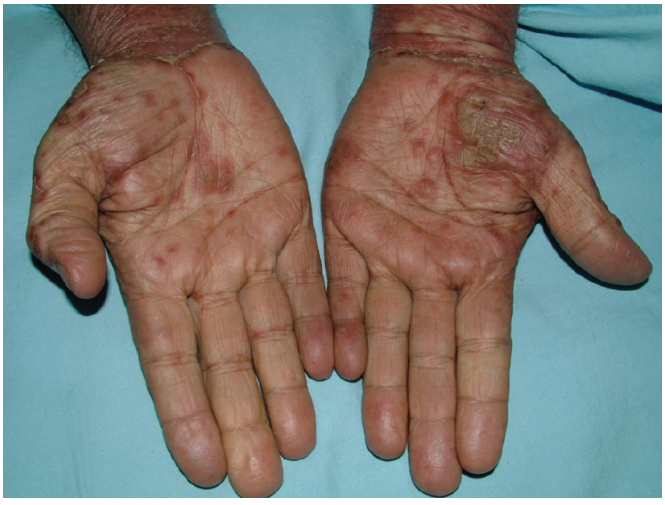

**Figure 12.** Clinical finding of pustular mycosis fungoides

MF is associated with poor prognosis.[51,52] Dermatologists should consider vesicular MF in the differential diagnosis of treatment-resistant eczematous skin lesions. If spongiosis and intraepidermal blisters are seen along with colonization by cerebriform lymphocytes on histopathological evaluation, vesicular MF must be considered to prevent delayed diagnosis or misdiagnosis.[52]

## Papular Mycosis Fungoides

A clinical variant characterized by small, non-folliculocentric papules. The classic patch and plaque stages of MF are not observed. Histopathologically, the findings are similar to those of classic MF, and a characteristic patch-like distribution is observed, without follicular involvement. Although it is known as a benign condition with long-term favorable prognosis, cases have been reported in which it progresses to erythroderma and tumor stage within a short period. Because of the lack of typical MF features, diagnosis can be challenging.[17]

## Solitary (Unilesional) Mycosis Fungoides

Characterized by an isolated macule, plaque, or nodule that cannot be distinguished histopathologically from classic MF. There are no other skin lesions. It is characterized by a band-like inflammatory infiltrate accompanied by isolated epidermal atypical lymphocytes. Histopathological findings suggest pagetoid reticulosis. The prognosis is good. It follows a benign course and rarely shows progression.[15]

## Invisible Mycosis Fungoides

In patients in whom the only symptom is itching, there are no visible lesions of MF. The diagnosis is based on histopathological findings.[53] As reported in the literature, MF is a significant imitator. In addition to the clinical subtypes mentioned above, numerous other MF subtypes have been described, including palmoplantar, psoriasiform, figurative erythema-like, verrucous, interstitial, anetoderma, and morphea-like. These subtypes exhibit clinical features similar to the diseases they mimic. Furthermore, MF may be observed in very different and unusual localizations. MF may involve the eyelids, mostly in the folliculotropic subtype and in advanced stage disease. The most common eyelid MF lesions are erythematous scaly patches or plaques. Diffuse thickening, edema, poikilodermic changes, atrophy, and wrinkling of the eyelids are other findings of MF. Milia-like papules, madarosis, and ectropion also occur in the folliculotropic variant of MF. The eyelids are also a typical localization site for tumoral MF, and their involvement is a poor prognostic indicator. Detection of eyelid involvement is important for early diagnosis.[54]

## Conclusion

It is essential to recognize the clinical features of both classical and variant forms of MF for early diagnosis and to consider the possibility of MF in the differential diagnosis. Dermatologists need to increase their awareness regarding this topic. Additionally, it should be kept in mind that diseases, such as psoriasis and eczema, may be observed together with MF or may develop later. In cases of resistance to treatment during the use of immunosuppressive or biological agents for eczema or psoriasis, biopsy should not be avoided. In cases in which histopathology is insufficient, *TCR* gene rearrangements, particularly NGS analysis, can be used.

### Footnotes

**Financial Disclosure:** The author declared that this study received no financial support.

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Review

# Differential Diagnosis of Mycosis Fungoides: A Review of Literature

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## Abstract

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, often experiences delayed diagnosis because of its ability to mimic numerous other conditions. Early-stage MF patches and plaques are frequently misdiagnosed as eczema, fungal infections, or psoriasis, leading to unnecessary treatments. However, the real challenge in differential diagnosis arises with MF's clinical variants and atypical localizations. The poikilodermatous variant may be confused with dermatomyositis and lupus erythematosus due to acquired poikiloderma; however, unlike these conditions, MF lesions typically occur in non-sun-exposed areas. MF presenting as pustules clinically resembles pustular psoriasis, subcorneal pustular dermatosis, and folliculitis. Atypical lymphocytes can induce follicular hyperkeratosis, which may lead to MF being mistaken for lichen spinulosus or keratosis pilaris. The bullous variant of MF can present with subcorneal, intraepidermal, or subepidermal vesicle bulla formation, resulting in lesions that resemble erythema multiforme, dyshidrotic eczema, or autoimmune bullous diseases. Both hyperpigmentation and hypopigmentation can be caused by MF. Hypopigmentation can mimic vitiligo, progressive macular hypomelanosis, and leprosy, whereas hyperpigmentation may resemble postinflammatory hyperpigmentation, lichen planus pigmentosus, pigmented actinic keratosis, and ashy dermatosis. Similar to systemic lymphomas, MF can also induce acquired ichthyosis, necessitating differentiation from both systemic and dermatological conditions that cause this skin disorder. In certain systemic lymphomas, such as MF, annular erythematous patches or plaques may develop. Histopathological examination is essential for distinguishing annular lesions that may clinically resemble erythema annular centrifugum, subacute lupus erythematosus, or juvenile annular lichenoid dermatitis. However, the clinical and histopathological findings of MF can vary significantly. When granulomatous infiltration is observed in the dermis, MF can be misdiagnosed as granuloma annular, sarcoidosis, leprosy, or acquired cutis laxa. Solitary erythematous papules, plaques, nodules, or alopecia may occur infrequently, and the differential diagnosis depends on the lesion's location. The urticarial variant, which is characterized by urticarial lesions, can be mistaken for urticarial drug reactions, T-cell leukemia, and lymphomas. When localized to the palmoplantar region, the condition can be confused with eczema, palmoplantar psoriasis, or palmoplantar keratoderma.

**Keywords:** Mycosis fungoides, poikiloderma, folliculitis, hypopigmentation, hyperpigmentation, blister, palmoplantar keratoderma, Woringer-Kolopp disease, granulomatous disease, granulomatous slack skin

## Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. The disease was first described by Jean-Louis Alibert, who observed that the lesions grow like mushrooms and eventually open like decaying fruit, emitting a foul odor.[1] Ernest Bazin later described the patch, plaque, and tumor stages of the disease, thereby naming this classical form of MF "Alibert-Bazin disease".[2] Besides the classical Alibert-Bazin type lesions observed in four stages-patch, plaque, tumor, and erythroderma-MF can present with various atypical skin manifestations. In 1938, Sézary and Yves Bouvrain identified large round or polygonal cells with large nuclei in both the skin and blood samples of an erythrodermic patient, leading to the characterization of the erythrodermic subtype.[3]

**Submission:** 02-Oct-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 27-Oct-2024

Access this article online

Quick Response Code:

**Website:** www.turkjdermatol.com

**DOI:** 10.4274/tjd.galenos.2024.49469

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**How to cite this article:** Tehçi T, Durdu M. Differential diagnosis of mycosis fungoides: a review of literature. Turk J Dermatol. 2025;19(1):19-26.

Because of its numerous variants, MF is considered a major mimicking disease, such as syphilis. Early-stage patch and plaque lesions of MF are clinically indistinguishable from inflammatory conditions like eczema and psoriasis. To differentiate these conditions, pathological and immunohistochemical examinations are required. However, in patients with MF in whom a diagnosis cannot be made, molecular biological methods such as polymerase chain reaction or Southern blot analysis are used to detect the monoclonality of the *T-cell receptor* gene.[4]

Dermoscopic examination is also very useful for differentiating MF from eczema and psoriasis lesions (Figure 1). In eczema, dermoscopy typically reveals vesicles, scale-crusts, and collar-like scales formed after vesicle rupture, while regular globular vascular structures are observed in psoriasis lesions.[5] For MF diagnosis, fine linear vessel structures and spermatozoa-like vessels are the most sensitive (93.7%) and specific (97.1%) findings.[6] Depending on the clinical type of MF, linear curved vessels, clustered punctate vessels, branching peripheral linear vessels, and red globular structures separated by white lines can also be detected by dermoscopy.[7]

Another important diagnostic method for distinguishing early-stage MF from psoriasis and eczema is high-frequency ultrasonography. Niu et al.[8] evaluated MF and clinically similar inflammatory diseases (psoriasis or eczema) using high-frequency ultrasonography and reported that epidermal thinning was highly sensitive (88%) and specific (75%) for distinguishing MF from psoriasis and eczema.

Early MF lesions can mimic dermatophytic infections (Figure 2). Dermoscopic examination revealed white-peeling scales, broken hairs, and follicular pustules as important clues for dermatophytic infections. Invasive dermatophytic infections, which are often observed in immunosuppressed patients, can also mimic tumoral MF lesions. These infections can be easily differentiated using direct microscopic examination, fungal culture, and various molecular diagnostic methods.[9]

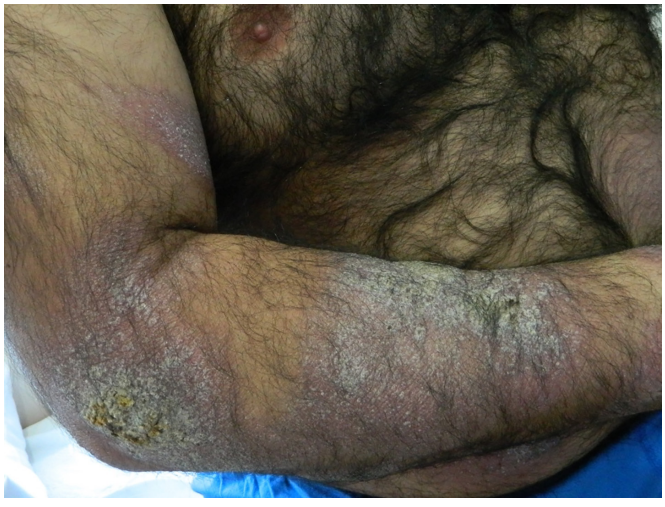

**Figure 1.** Psoriasis-like erythematous scaly plaques on the upper extremities of a patient with mycosis fungoides

## Differential Diagnosis of Mycosis Fungoides Variants

**Poikilodermatous mycosis fungoides:** This variant is characterized by more pronounced epidermal atrophy, telangiectasia, and widespread or isolated hypo- and hyperpigmentation (Figure 3). Poikiloderma is not a clinical manifestation specific to a single disease. Connective tissue diseases such as lupus erythematosus and dermatomyositis, Civatte Poikiloderma, excessive use of topical glucocorticoids, radiation dermatitis, graft-versus-host disease, and certain genodermatosis such as Rothmund-Thomson syndrome can cause poikiloderma. In MF, poikilodermatous lesions are localized to flexural areas and sun-protected regions of the trunk, whereas in connective tissue diseases, they appear in sun-exposed areas. For a definitive diagnosis, histopathological

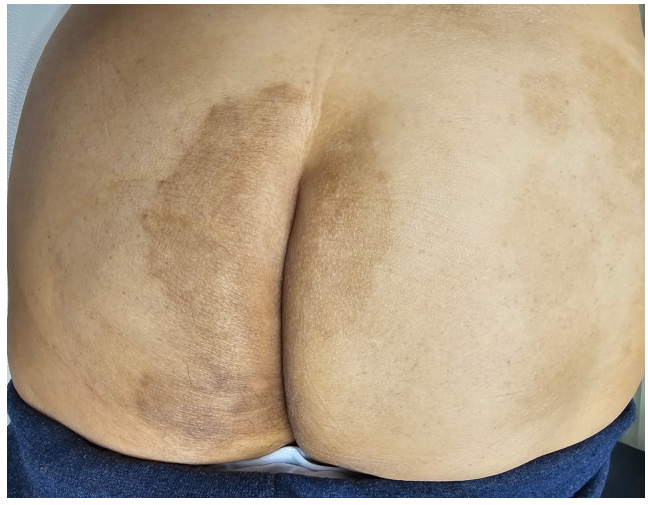

**Figure 2.** Erythematous scaly patches on the gluteal region of a patient with mycosis fungoides, mimicking dermatophytic infections

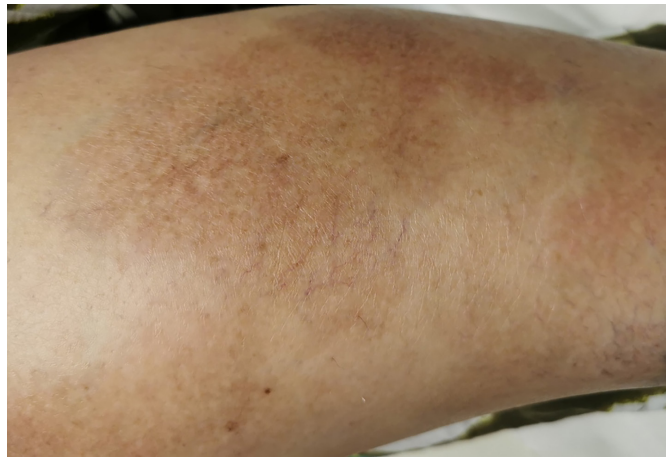

**Figure 3.** Poikilodermatous patch on the upper extremities of a patient with mycosis fungoides

examination should reveal epidermal atrophy, pigment loss with mild to moderate vacuolar degeneration in the basal layer, increased melanophage in the papillary and upper reticular dermis, epidermotropism, Pautrier microabscesses, vascular ectasia, and proliferation.[10] Rarely, granulomatous dermatitis and syringotropic may also be observed in poikilodermatous MF lesions upon histopathological examination.[11,12] In MF patients, vascular ectasia without atrophy and pigmentation changes may also be observed. This clinical form is called telangiectatic MF. These telangiectasias, which may be unilateral or localized, can be confused with unilateral nevoid telangiectasia or the linear form of telangiectasia macularis eruptiva perstans.[13,14] When erythrocyte extravasation and hemosiderin deposition occur in the dermis due to secondary endothelial cell proliferation caused by T-lymphocytes in MF, it leads to purpuric lesions resembling pigmented purpuric dermatosis (PPD).[15] Although not specific, dermoscopic examination of pigmented MF lesions reveals short, fine, linear vessels and spermatozoa-like structures, whereas in PPD lesions, dull red and reticular pigmentation with erythematous globules are observed. Differentiating between MF and PPD is challenging both clinically and histologically. In 1994, Ackerman compared the histopathological features of PPD and MF and noted many similarities between the two.[16] FOXP3 positivity has been reported in PMF cases. A positive and statistically significant correlation was found between FOXP3 expression in the dermis and the response to the treatment score. Higher FOXP3 levels in the dermis predict a more severe disease course and poorer response to treatment, including longer time to remission, higher chance of relapse, and shorter remission. A negative and non-significant correlation was found between FOXP3 expression in the epidermis and stage severity.[17]

**Pustular and follicular mycosis fungoides:** Pustular MF refers to an extremely rare clinicopathologic variant of MF, initially described by Ackerman et al.[18] as a chronic vesiculopustular eruption that gradually transforms into typical MF plaques. The pustules may become widespread or confined to the palmoplantar region.[18,19] Histopathological examination revealed typical MF features, such as band-like infiltrates of atypical lymphocytes, epidermotropism, and Pautrier microabscesses, along with subcorneal pustules containing atypical lymphocytes, neutrophils, and eosinophils. These lesions can be confused with pustular psoriasis and subcorneal pustular dermatosis.[20] Additionally, the development of eosinophilic folliculitis due to hematologic malignancies has been reported. In one case reported in the literature, intense perifollicular infiltration rich in lymphocytes and eosinophils was observed in an MF patient.[21] It should also be noted that the presence of pustular lesions is associated with an increased risk of transformation and systemic involvement.[22] *Staphylococcus aureus (S. aureus)* superantigen are known to stimulate T-cells. *S. aureus* colonization is closely associated with clinical deterioration in patients with MF. Therefore, the presence of *Staphylococcus* should be investigated via culture in the presence of pustules. Recent data support this by showing that antibiotics inhibit malignant T-cells in skin lesions of MF and Sézary syndrome.[23,24] The typical clinical features of folliculotropic MF include hardened erythematous plaques combined with acneiform lesions, including follicular papules, small cysts, and comedones located on the head and neck. These papulopustular lesions can be confused with folliculitis, acne, and alopecias (Figures 4, 5).[25] In folliculotropic MF, follicular plugs, perifollicular white areas, and hair loss are observed.[26] When follicular MF leads to spiny projections on the skin, it can be mistaken for keratosis pilaris and lichen spinulosus.[27] Another common finding of follicular MF is follicular mucinosis, which is characterized by mucinous degeneration of the follicular epithelium, which is more apparent with Alcian blue or other mesenchymal

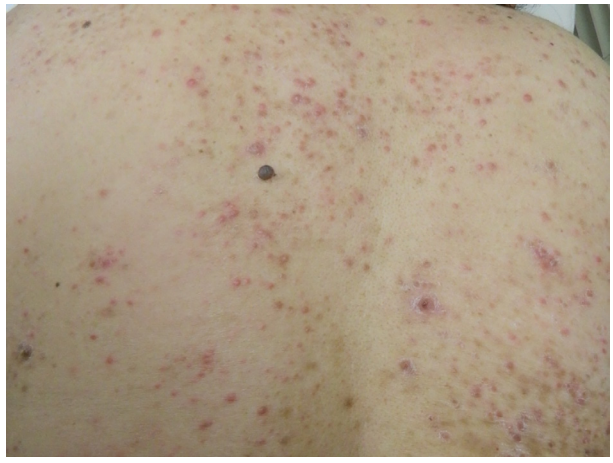

**Figure 4.** Follicular erythematous papules and nodules on the back of a patient with follicular mycosis fungoides

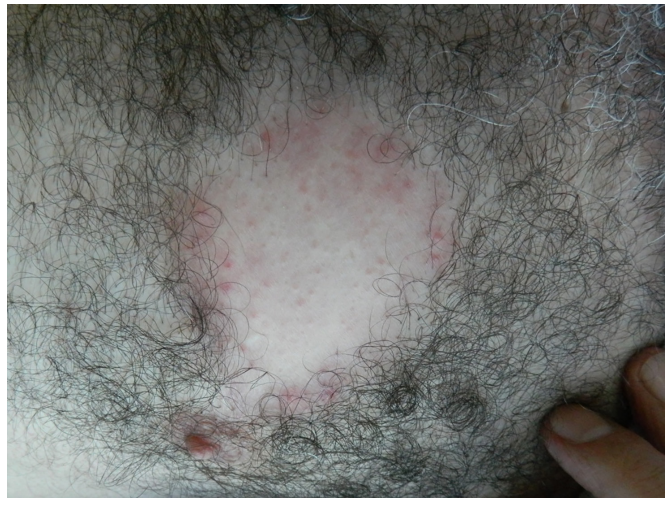

**Figure 5.** Alopecic patch on the front of the chest in a patient with follicular mycosis fungoides

mucin stains.[25] The intensely pruritic lesions of folliculotropic MF indicate poor prognosis, similar to tumoral MF.[28]

**Vesiculobullous mycosis fungoides:** In the classic form of MF, vesiculation is not observed clinically or histopathologically. However, in rare cases, subcorneal, intraepidermal, or subepidermal vesicle bulla formation may occur in patients with MF. This type, which is characterized by bullous-vesicular lesions, has a poor prognosis, with a 1-year survival rate of approximately 50% following the onset of bullous lesions.[29] These lesions typically appear as tense or flaccid bullae located on the trunk and extremities (Figure 6). Flaccid bullae may occasionally exhibit Nikolsky positivity.[30] While diagnosis is straightforward when bullae accompany classic MF lesions, diagnosis becomes challenging in the presence of isolated bullae. The average time to diagnosis for these patients is 6-7 years. One case report described a delay in diagnosis of up to 40 years due to the disease mimicking autoimmune bullous diseases, erythema multiforme, and dyshidrotic eczema.[31,32] The term "dyshidrotic MF" has been used to describe bullae limited to the palms and soles.[33] It should also be remembered that not only MF but also adult T-cell leukemia/lymphomas can present with findings similar to those of dyshidrotic eczema.[34] Bullous lesions are rarely associated with Sézary syndrome. This bullae may be due to MF itself or secondary to phototherapy used in the treatment of the disease. When bullous lesions develop, especially in elderly patients with MF, immunofluorescence studies should be conducted to rule out concomitant autoimmune bullous diseases, such as bullous pemphigoid.[35] Patients with MF are at risk of herpes simplex virus infection because of decreased cellular immunity and weakened skin barrier. Bullous MF lesions may also occur due to these infections. The tzanck smear test, which is the fastest and most practical test, can be used to differentiate vesiculobullous lesions.[36]

**Hypo/hyperpigmented mycosis fungoides:** Although atypical forms of MF generally have a poor prognosis, hyperpigmented MF, which has predominantly been reported in individuals with darker skin tones, is rarely progressive.[37] More than half of this type of MF, which can be confused with postinflammatory hyperpigmentation, pigmented actinic keratosis, lichen planus pigmentosus, and ashy dermatosis, is associated with CD8+ cytotoxic T-lymphocytes (Figure 7).[38] Hypopigmented MF, which also mostly arises due to CD8+ cytotoxic T-lymphocytes, can be confused with diseases causing hypopigmentation, such as vitiligo, progressive macular hypomelanosis, and leprosy. The onset age of hypopigmented MF is earlier than that of classic MF. The onset age of classic MF is between 55 and 60 years, whereas hypopigmented MF typically occurs during pediatric and early adult periods.[39] In hypopigmented MF, patch-stage MF findings are accompanied by pigment loss in the basal layer, which can be observed with MART-1 staining.[40,41]

**Ichthyosiform mycosis fungoides:** Several diseases can cause congenital or acquired ichthyosis of the skin. Although congenital forms arise from different genetic mutations, acquired forms can be secondary to certain systemic diseases, medications, skin conditions, and lymphomas. Ichthyosiform MF is a rare clinical variant of MF, accounting for approximately 3.5% of cases. Diagnosis is straightforward when ichthyosis accompanies classic MF lesions, but in patients presenting with only ichthyosis, its diagnosis may be delayed.[42] Moreover, adult T-cell leukemia/lymphomas should also be ruled out in such cases.[43]

**Annular mycosis fungoides:** When MF lesions exhibit an annular pattern, they can be confused with diseases that cause figurate erythema, such as erythema annular centrifugum, Jessner's lymphocytic infiltration, annular psoriasis, subacute lupus erythematosus, or juvenile annular lichenoid dermatitis. In rare instances, they may mimic erythema gyratum repens by forming interlocking erythematous rings (Figure 8).[44,45] Annular lesions can also be observed in other types of lymphomas. In patients with follicular lymphoma, the development of annular lesions may indicate transformation into diffuse large B-cell lymphoma.[46]

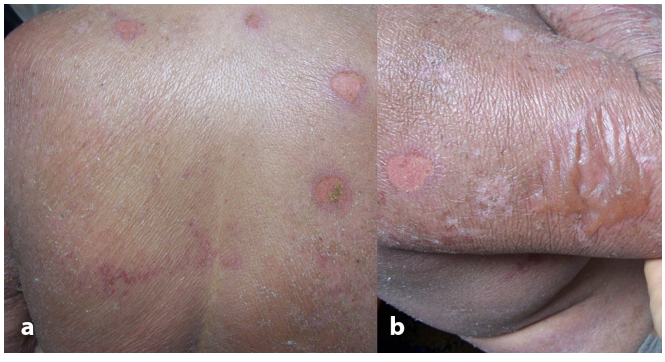


**Figure 6.** (a,b) Eroded areas and bullae on the back and extremities of a patient with erythrodermic mycosis fungoides

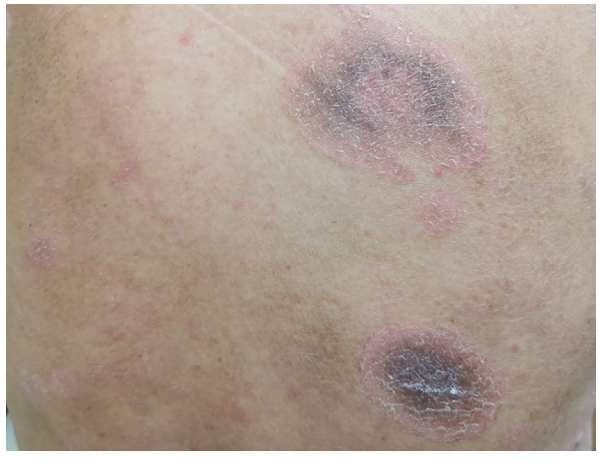

**Figure 7.** Hyperpigmented patches resembling fixed drug eruptions on the back of a patient with hyperpigmented mycosis fungoides

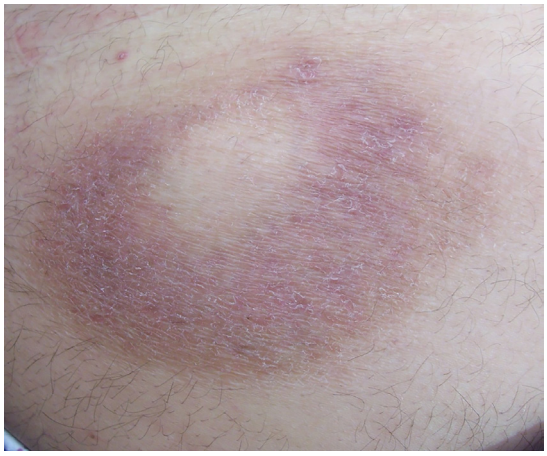

**Figure 8.** Annular erythema annulare centrifugum-like plaque on the lower abdomen of a patient with mycosis fungoides

**Granulomatous mycosis fungoides:** Granulomatous MF is a histopathological variant that should be diagnosed through skin biopsy. Findings include perivascular granulomas along with atypical lymphocytes, histiocytes, and multinucleated giant cells in the dermis. Epidermotropism is observed in approximately 50% of cases, thereby complicating diagnosis in patients without characteristic clinical symptoms.[47] Histopathological findings of this form can be confused with granuloma annularis, sarcoidosis, and leprosy. This variant has a poor prognosis and is associated with a high risk of secondary lymphoma.[48] Granulomatous slack skin syndrome, which has unique clinical and histopathological features, is distinct from granulomatous MF.[49] Clinically, these patients present with sagging skin in the axillary or inguinal regions, and histopathological examination reveals prominent elastophagocytosis, differentiating it from granulomatous MF. Dermoscopy revealed pale-orange areas corresponding to granuloma structures on an erythematous background, alongside fine linear vascular structures.[50] Granulomatous slack skin can be confused with hematologic diseases that cause acquired cutis laxa,[51] and many patients develop secondary lymphoma in the advanced stages.[49]

**Urticarial mycosis fungoides:** This extremely rare form of MF is characterized by typical urticarial lesions accompanied by severe pruritus and peripheral blood involvement. It has a favorable prognosis and responds rapidly to treatment. In addition to classic MF findings, histopathology revealed CD25 and FOXP3 positivity on immunophenotyping. Differential diagnoses include urticarial lymphomatoid drug reactions, T-cell prolymphocytic leukemia, Sézary syndrome, and other lymphomas, such as adult T-cell lymphocytic leukemia. This factor should be considered in the differential diagnosis of treatment-resistant urticarial lesions.[52]

**Verrucous mycosis fungoides:** Verrucous MF, the least common of its morphological variants, may appear similar to warts, deep fungal infections, seborrheic keratoses or other conditions rather than a neoplastic entity with potentially serious consequences for the patient. The overall incidence of verrucous MF is unknown, and reported cases to date are rare. Verrucous MF lesions are usually asymptomatic and rarely pruritic.[53,54]

**Solitary or localized mycosis fungoides:** This is one of the forms of MF with a good prognosis. It is characterized by isolated macules, plaques, or nodules that have histopathological features that are indistinguishable from those of classic MF. This extremely rare form can also present as an alopecic patch. Depending on the location of the lesions may mimic different diseases (Figure 8). An erythematous plaque localized around the eye may be mistaken for an erysipelas, whereas a nodule in the umbilical region may be confused with a Sister Mary Joseph nodule.[55] Because nodules in the umbilical region can also occur in systemic lymphomas other than MF, immunohistochemical staining should be performed.[56,57] In the 2005 WHO/EORTC lymphoma classification, Woringer-Kolopp disease was classified as a solitary variant of MF. Consequently, most solitary MF cases in the literature have been evaluated as Woringer-Kolopp disease (also known as localized pagetoid reticulosis), which is characterized by slow growth, slow clinical progression, and favorable prognosis. Clinically, it usually presents as a solitary lesion in the acral regions of the extremities. The lesion typically presents as a psoriasiform, hyperkeratotic, erythematous plaque.[55]

Characteristic histopathological findings of pagetoid reticulosis include prominent epidermotropism with an infiltrate of atypical pagetoid lymphocytes, characterized by large and hyperchromatic nuclei surrounded by a pale halo, and epidermal hyperplasia with parakeratosis. Pagetoid reticulosis is typically characterized by a CD8+ immunophenotype, often accompanied by CD30 expression.[58] In contrast, solitary MF may show classical histopathological features along with folliculotropic or syringotropism.[53] Solitary MF can also be confused with CD4+ small/medium-sized pleomorphic T-cell lymphoma and CD8+ lymphoproliferative disorder of the ear/face, both clinically and histopathologically. Although dermal atypical lymphocytes are not observed in Woringer-Kolopp disease, CD8+ lymphoproliferative disorder of the ear/face is characterized by a dense dermal infiltration of monomorphic medium-sized atypical lymphocytes, with less than 5% large cells.[59]

Although MF typically localizes to non-sun-exposed areas, in some patients, it may localize to acral regions, mimicking eczema, palmoplantar psoriasis, and palmoplantar keratoderma. If not considered in the differential diagnosis, patients may use topical keratolytic drugs or steroid creams for years.[60] Syringotropic MF is a rare clinicopathologic variant

of MF characterized by eccrine gland involvement. Clinical findings include erythematous papules and plaques that may or may not be associated with follicular eruptions. Adnexal involvement frequently leads to anhidrosis and alopecia.[61] The condition can be confused with punctate keratoderma when palmoplantar involvement is present.[62] When localized to sun-exposed areas, it may mimic chronic actinic dermatitis, and when located at the corner of the lips, it may be mistaken for angular cheilitis.[62,63] Mucosal involvement is rare in MF and is a poor prognostic indicator. The majority of patients die within 3 years of the discovery of mucosal involvement. Oral mucosal involvement was observed in 18.6% of patients with MF who underwent autopsy. Patients with MF should be carefully evaluated for oral, genital, and nasal mucosal symptoms. Mucosal involvement mimics many benign inflammatory conditions and malignant diseases both clinically and microscopically.[64,65] Rarely, when it develops without cutaneous manifestations, it may present as a geographic tongue-like appearance.[66]

## Conclusion

MF mimics many dermatological diseases because of its wide range of clinical manifestations. For early diagnosis, the disease should be considered, and close collaboration with pathologists is essential.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: T.T., M.D., Concept: T.T., M.D., Design: T.T., M.D., Data Collection or Processing: T.T., M.D., Analysis or Interpretation: T.T., M.D., Literature Search: T.T., M.D., Writing: T.T., M.D.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Review

# Histopathological Diagnosis of Mycosis Fungoides

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## Abstract

Mycosis fungoides (MF) is a neoplastic proliferation characterized by cutaneous infiltration of atypical T-lymphocytes. MF often shows diagnostic difficulties. Histopathology, immunochemistry, and clonality determination may be an auxiliary diagnostic method but they are not always sufficient and the final diagnosis should be made with correlation of clinical findings, routine histopathology, immunohistochemistry, and gene rearrangement studies. Histopathological findings may also vary in different stages of the disease. In this article, the histopathological findings of classical MF and its variants are reviewed together with their immunohistochemical features.

**Keywords:** Mycosis fungoides, tumor, MF

## Introduction

Mycosis fungoides (MF) is a neoplastic proliferation characterized by cutaneous infiltration of small to medium-sized T-lymphocytes. The clinical and histopathological diagnosis of MF is not always easy. A discordance rate as high as 48% has been reported among pathologists for the diagnosis of early MF.[1] MF often shows diagnostic difficulties, due to its absence of specific features, different types of clinical lesions, and mimicking some benign inflammatory disorders. In addition to histopathology and immunochemistry, clonality determination may be an auxiliary diagnostic method for MF. Although almost all cases of MF are characterized by monoclonal proliferation of $CD4^+$ cells, monoclonality may be seen in apparently non-neoplastic conditions, such as pityriasis lichenoides acuta, lichen aureus, lichen planus, pigmented purpuric dermatosis, allergic contact dermatitis, and drug reactions. Therefore, detection of monoclonality is not sufficient for diagnosis of MF.[2] Another problem in the diagnosis is that different local treatments may alter the histopathological findings. Generally, it is advisable to take multiple biopsies from morphologically different lesions, to repeat biopsies after a 2-week washout period from local treatment, and to perform re-biopsies on recurrent lesions. Repeat biopsies on recurrent lesions might be useful to show if histopathologic features are stable or changing.[3] Considering all these problems, despite the well-defined histologic findings, the final diagnosis of MF should be made with correlation of clinical findings, routine histopathology, immunohistochemistry, and gene rearrangement studies.

### Histopathological Features

#### Patch Stage

The histopathological features of the early patch stage of MF are usually subtle and easily overlooked. Vast majority of cases reveal a patchy-lichenoid or band-like infiltrate in an expanded, partly fibrotic papillary dermis (Figure 1). The epidermis may be hyperplastic, normal, or atrophic, and the pattern may be different in different biopsies taken on the same day (Figures 2, 3). Epidermotropism that is characterised by the colonisation of epidermis by T-lymphocyte is a histologic hallmark for MF. Within the epidermis, there are characteristically small numbers of atypical irregular

**Submission:** 07-Nov-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 25-Jan-2025

Access this article online

Quick Response Code:

**Website:** www.turkjdermatol.com

**DOI:** 10.4274/tjd.galenos.2025.03521

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**How to cite this article:** Gülseren D. Histopathological diagnosis of mycosis fungoides. Turk J Dermatol. 2025;19(1):27-35.

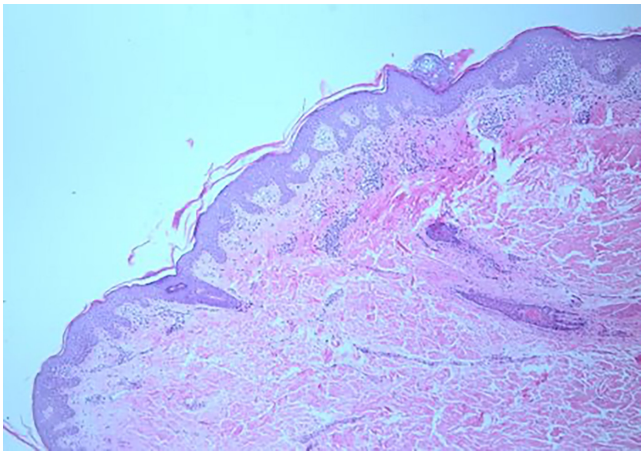

**Figure 1.** Patchy-lichenoid infiltrate in patch stage mycosis fungoides

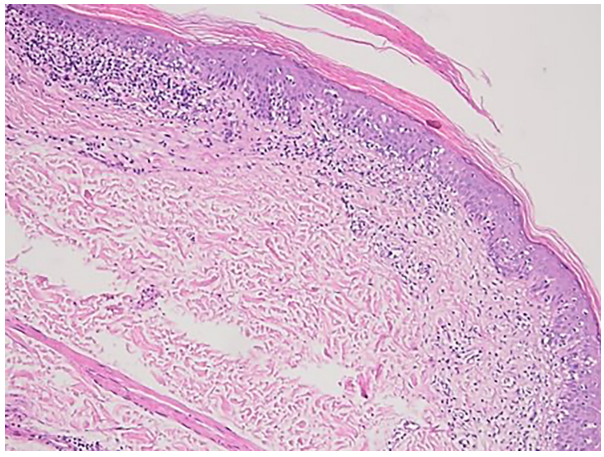

**Figure 2.** Atrophic epidermis with hyper- and parakeratosis

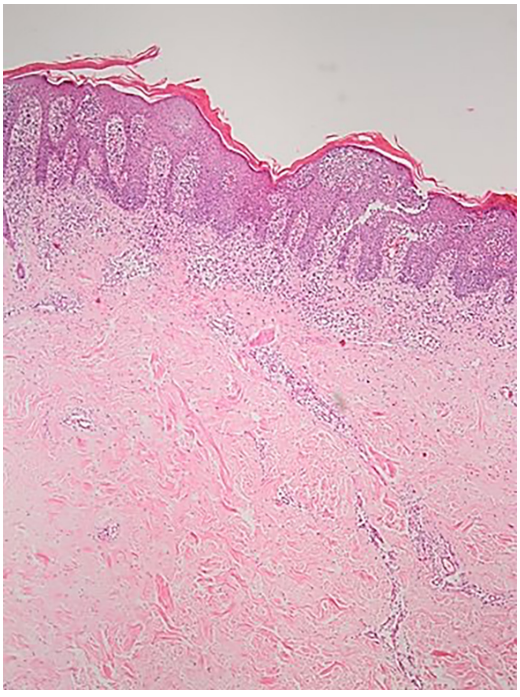

**Figure 3.** Epidermal hyperplasia and elongation of rete ridges

lymphoid cells, each surrounded by a clear halo, although in very early lesions they may sometimes be absent. The nuclei of epidermotropic lymphocytes are slightly larger than those of lymphocytes within the upper dermis. Basillar epidermotropism that is characterized by the presence of lymphocytes aligned along the basal layer of the epidermis is another diagnostic clue for MF (Figures 4, 5).[3] The Pautrier microabscess (sharply marginated discrete clusters of lymphocytes in close apposition with one another, within the epidermis) is, when strictly defined, highly characteristic of MF (Figure 6). They are uncommon in the patch stage, however, and if this feature is given undue importance, many cases of MF will be missed.[4,5] On the other hand, large Pautrier microabscesses and atypical dermal lymphocytes in early lesions are associated with progression to an advanced disease stage.[6] There is a relatively sparse infiltrate of lymphocytes spread along the slightly expanded papillary dermis with little tendency to aggregate around vessels of the superficial plexus. Eosinophils and plasma cells are present in small numbers or absent. Red cell extravasation and pigmentary incontinence can be observed. Other dermal findings of patch stage MF

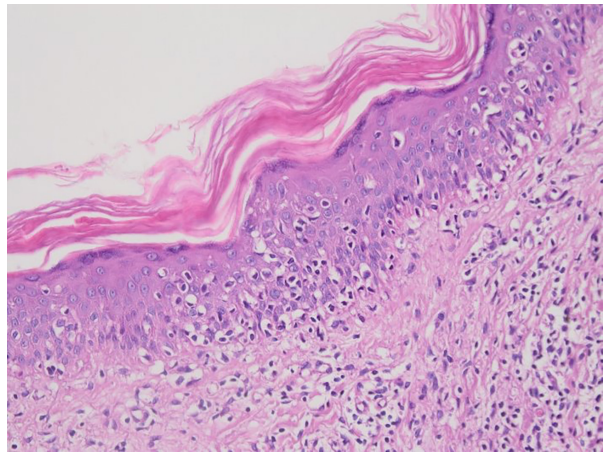

**Figure 4.** Colonisation of epidermis and basal layer with atypical, haloed lymphocytes

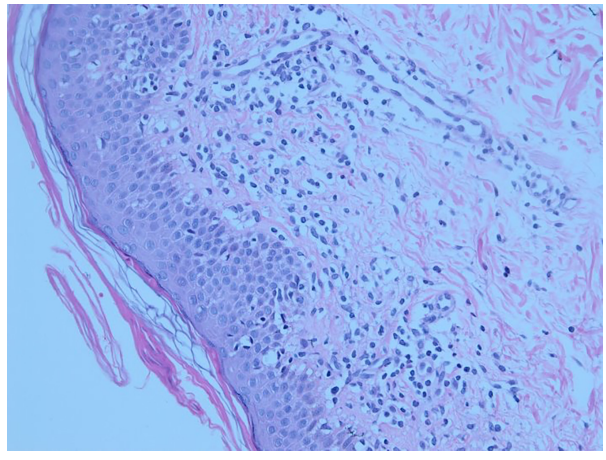

**Figure 5.** Irregular epidermal and dermal lymphocytes with clear halo formation and fine, fibrillary collagen bundles in dermal papilla

are related to fibrotic changes elicited by chronically retained neoplastic cells in the papillary dermis ("signs of chronicity"). These changes typically occur in late but not in early patch stage MF and include: (1) conversion of the papillary dermal collagen from fine fibrillary forms into wiry collagen bundles (fettuccine-like fibrosis) and (2) "halo" formation around lymphocytes.[4,5,7,8]

In addition to the classical features of MF described above, angiocentricity have been reported in limited cases. MF with angiocentric features should be differentiated from extranodal T/NK-cell lymphoma, cutaneous γ/δ T-cell lymphoma, anaplastic large-cell lymphoma, and adult T-cell leukemia/lymphoma and lymphomatoid papulosis type E, in which angiocentricity is common.[9]

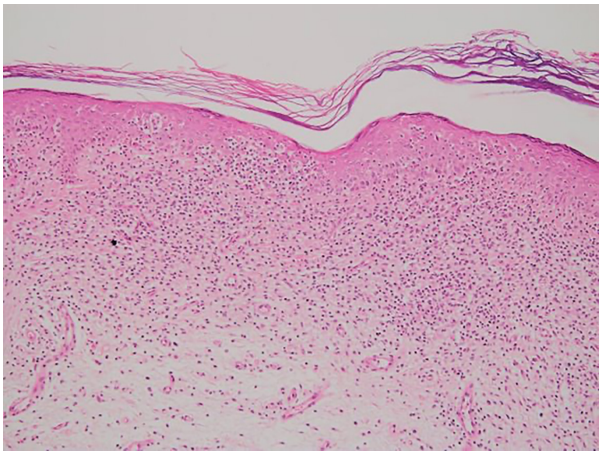

**Figure 6.** Pautrier microabscess composed of discrete clusters of lymphocytes in the epidermis

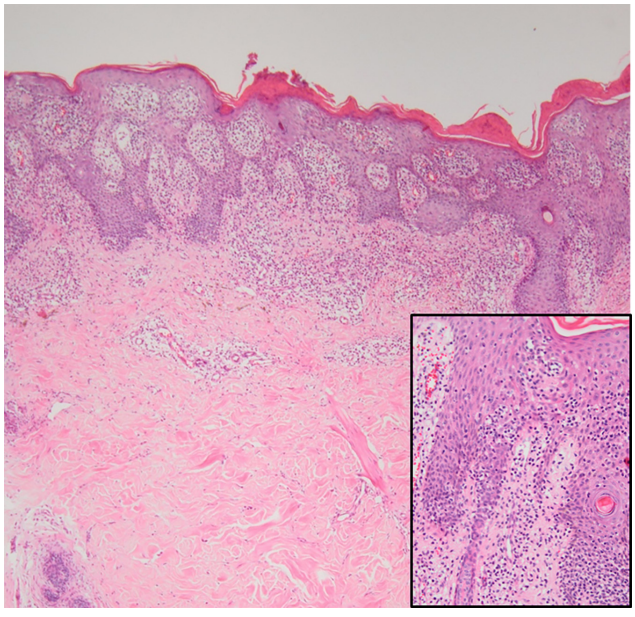

**Figure 7.** Broad, band-like infiltrates extending into the superficial reticular dermis in plaque stage disease

## Plaque Stage

In plaques of MF, the infiltrate is more dense and atypical lymphocytes are more common. The lymphocytes measure 10 to 30 μm in diameter, and their nuclei are often obviously indented, prune-like or cerebriform.[10] Neoplastic T-cells form broad, band-like infiltrates that extend from the papillary into the superficial reticular dermiş (Figure 7). In both the plaque and tumor stages, it is not infrequent to observe admixed inflammatory cells, such as eosinophils and plasma cells. This is likely a consequence of a switch in immune effector function from $T_H1$ to $T_H2$ during disease progression. Pautrier microabscesses are not uncommon, being identified in 17-37.5% of cases.[11] Coarse collagen bundles with or without increased numbers of fibroblasts are commonly present in the papillary dermis.[12]

## Tumor Stage

The lesions are often ulcerated in the tumor stage. Pautrier microabscesses are uncommon.[12] The clinical emergence of tumors and nodules at late disease stages correlates with loss of epidermotropism and nodular or sheet-like expansion of neoplastic T-cells in the reticular dermis, sometimes extending into the subcutaneous fat (Figure 8).[11] Syringotropism may be the predominant pattern of infiltration with invasion of components of the eccrine coil and duct sometimes associated with proliferation of the epithelial structures. Syringotropism can also accompany either epidermal or follicular involvement.[13]

## Large Cell Transformation

Large cell transformation in MF is defined as the presence of large cells exceeding 25% of the infiltrate or of large cells forming microscopic nodules and has been detected in more than 50% of patients with tumor-stage MF.[14] Large

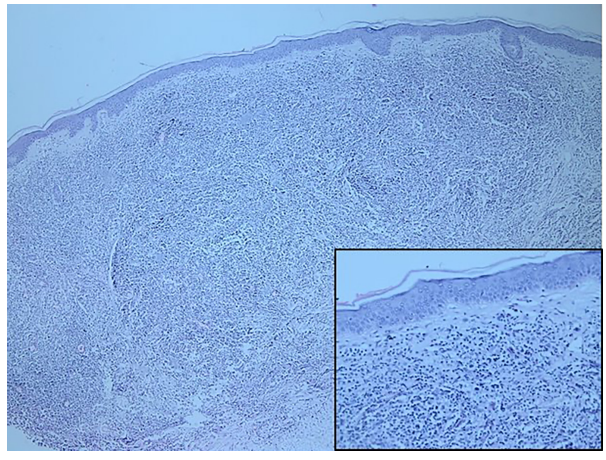

**Figure 8.** Loss of epidermotropism and nodular expansion of neoplastic lymphocytes extending subcutaneous fat in tumor stage disease

cells are defined as being four or more times the size of a small lymphocyte. They have prominent vesicular or hyperchromatic nuclei, often with conspicuous nucleoli and abundant cytoplasm. Nuclear pleomorphism is common, and giant cells (including Reed-Sternberg-like variants) are sometimes present. Mitotic activity is usually marked and abnormal forms may be identified.[12] Transformation is associated with a very poor prognosis and predicts for inferior outcome even in patients with advance stage disease. Median survival from transformation ranges from 11 to 36 months.[14-16] Differentiating MF with large cell transformation from primary cutaneous anaplastic T-cell lymphoma is histologically unfeasible, and requires immunophenotyping and clinical correlation with preexisting patches or plaques.[17] A high Ki-67 index and positivity for p53 have been reported as useful in confirming large cell transformation in MF.[18] However, large cell transformation should be diagnosed exclusively according to the histopathological-morphological features.[3]

## Immunophenotype

MF is commonly characterized by the infiltrate of $CD4^+$, CD45RO-positive helper/memory T-lymphocytes, although less frequently a $CD8^+$ and even CD4/CD8-phenotypes may be seen. The latter has no prognostic significance. The lymphocytes usually also be expected to express the pan-T-cell antigens CD2, CD3, CD5, and CD7, as well as TCRαβ and cutaneous lymphocyte antigen. CD7 is often focally lost in early stages, and its loss is not specific for MF as its expression is also often lost in reactive conditions

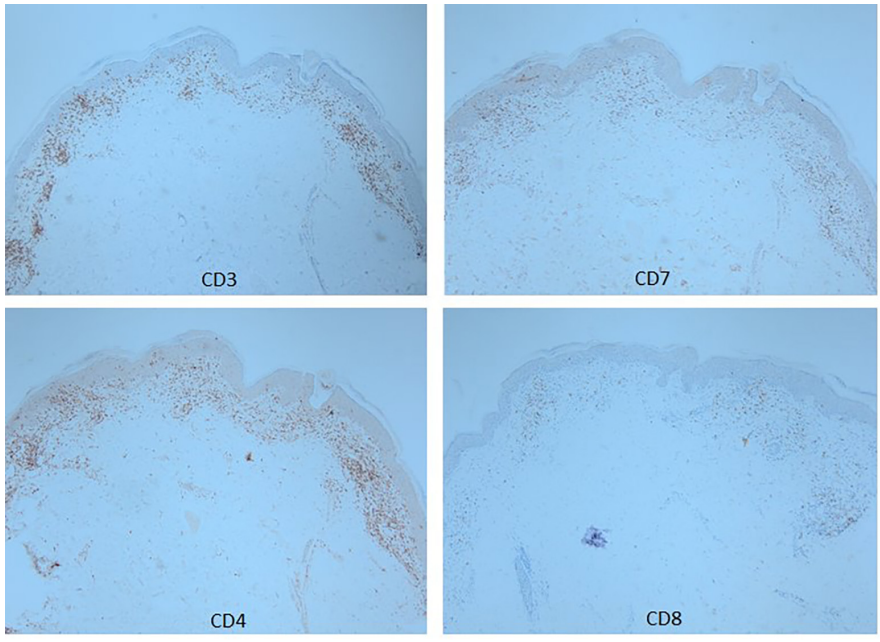


**Figure 9.** Minimal CD7 loss and further lack of CD8 expression

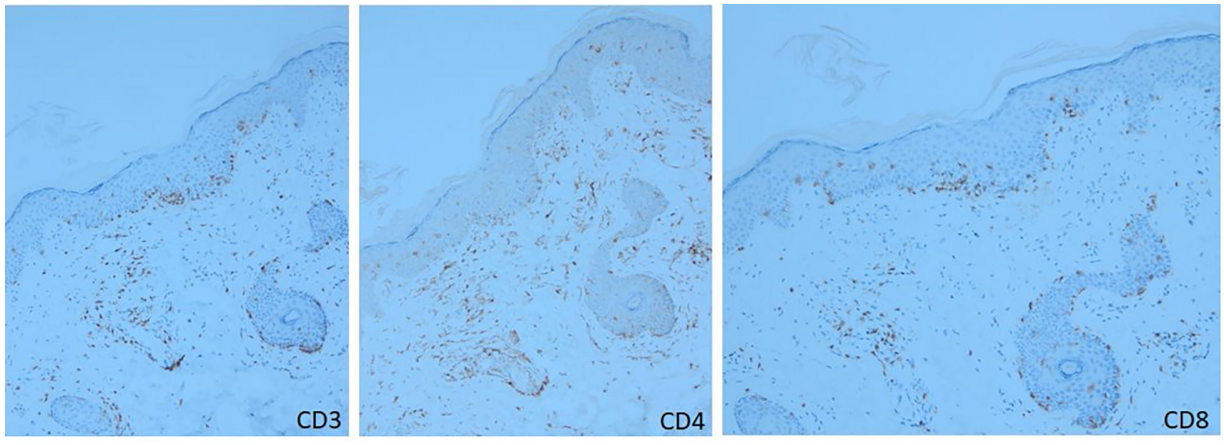


**Figure 10.** Immunohistochemical phenotype with CD8 expression in patch stage mycosis fungoides

(Figures 9, 10). CD25 (interleukin-2 receptor) and the T-follicular helper cell marker, PD1, are also frequently expressed. Transformed cases may express CD30 but has no prognostic implications. Unlike some other cutaneous T-cell lymphomas, MUM1 is not frequently expressed. Abnormal expression of CD20, apart from other B-cell markers, is occasionally seen and indicates a progressive course associated with poor prognosis.[19] Progression of MF is accompanied by a switch from $T_H1$ and $T_H2$ cytokine expression: epidermal $T_H1$ cytokine profiles characterize patch and plaque stages, whereas $T_H2$ cytokine profiles dominate tumor stages.[12] CD56 expression has been reported very rarely in MF. $CD56^+$ MF shows cytotoxic interface dermatitis with basal hydropic degeneration, pigment incontinence and telangiectasia and its expression has been associated with indolent course.[20]

The immunophenotype of transformed MF is similar to prototypical MF, although there is more frequent loss of CD7, CD2, and CD5. The transformed tumor cell population is typically $CD4^+$ although these may acquire a cytotoxic phenotype with expression of cytotoxic molecules such as TIA-1, perforin, and granzyme B. Exceptionally, $CD8^+$ variants have been described. Some degree of CD30 expression is seen in 30-50% of cases, and in half of these, 75% of the infiltrate express this antigen. Expression of CD30 is not associated with prognosis. CD25 expression is also seen in many cases.[15,16,21]

Determination of a clonal T-cell receptor gene rearrangement may be identified by Southern blot or polymerase chain reaction (PCR) in the majority of cases. In general, monoclonality can be expected in up to 100% of tumor stage cases, 50-100% of plaque-stage cases, and 50-78% of patch-stage MF cases.[22] However, the results should be interpreted with caution, as monoclonal *TCR* gene rearrangements have been identified in a number of inflammatory dermatoses, including discoid lupus erythematosus, lichen planus, lichen sclerosus, and pityriasis lichenoides et varioliformis acuta.[23-29] More recently, targeted next-generation sequencing (t-NGS) technologies have been developed to detect *TCR* gene rearrangements and somatic mutations. t-NGS provided a reliable basis for T-cell lymphoma diagnosis in samples with partially degraded DNA that was impossible to assess with PCR. Despite the fact that T-cell clonality assessment by PCR appears to be less specific and requires higher quality DNA than t-NGS, both techniques remain complementary because PCR recovers some t-NGS-negative cases. The design of a single t-NGS test encompassing both clonal rearrangements of *TCR* genes and mutational status of target genes may represent an attractive alternative to conventional multiplex PCR in the near future.[30]

## Variants Listed Under the WHO/EORTC Classification

### Folliculotropic Mycosis Fungoides

There is a follicular and perifollicular infiltrate of small to medium-sized lymphocytes with cerebriform nuclei. The infiltrate may also be present around vessels and the eccrine apparatus, sometimes extending into eccrine epithelium in a similar manner to that in the follicle. Mucin may be minimal or form small pools in the follicular epithelium (Figure 11). In addition to follicular deposition, mucin may also be detected epidermally or dermally in classical MF and is suggested to originate from factor XIIIa- and CD34-positive dermal dendrocytes in response to tissue damage and inflammation.[31] Pautrier microabscesses are occasionally present. Involvement of the epidermis is not present or is minimal. Granulomatous inflammation is usually secondary to ruptured hair follicles.[32-34] Early folliculotropic MF may present with spiky/keratosis-pilaris-like lesions on the trunk and extremities and it usually has excellent prognosis. The level of the lymphoid infiltrate along the hair follicle is more superficial and limited to the infundibulum, without nodule formation.[35] The atypical lymphocytes have $CD3^+$, $CD4^+$, $CD8^-$ phenotype (Figure 12). Scattered large atypical $CD30^+$ or $CD30^-$ cells are commonly seen, and they may become more confluent in large cell transformation.[10]

### Pagetoid Reticulosis

The epidermis shows a psoriasiform appearance in association with hyperkeratosis and/or parakeratosis and acanthosis. The epidermal infiltrate is characterised by medium to large lymphocytes with large and irregular nuclei and pale eosinophilic cytoplasm. A perinuclear halo is commonly present. Cells are arranged singly or in nests or clusters and they show Pautrier microabscess-like configurations, or be present in large lacunae.[36,37] Atypical cells are present at all levels of the epidermis but are most prominent in the lower third. Cells in the upper layers of the epidermis may show subtle degenerative changes. There are conspicuous mitotic figures. Involvement of adnexal epithelium is often a feature.[10] The superficial dermis contains a perivascular lymphohistiocytic infiltrate, but atypical cells are very sparse or absent. Three different phenotypes have been described with decreasing frequency of $CD8^+$, $CD4^+$, and $CD4^-CD8^-$ cases. Both $CD4^+$ and $CD8^+$ variants express βF1, whereas rare cases of CD4/CD8 double negative cases show γ/δ TCR expression.[36,38,39] CD4/CD8 double negative pagetoid reticulosis cases appear to have higher Ki-67 proliferative index, but, in contrast to primary cutaneous γ/δ T-cell lymphomas, this phenotype does not appear to confer poor prognosis.[38] Most pagetoid reticulosis cases express pan-T-cell antigens CD3, CD2, and CD5, but typically lack CD7 expression and, in some cases, CD45

(leukocyte common antigen). TIA-1 and CD30 expression by a significant proportion of $CD8^+$ pagetoid reticulosis has been described.[36,38]

## Granulomatous Slack Skin

Early lesions exhibit a superficial, or superficial and deep, perivascular lymphocytoid infiltrate; psoriasiform epidermal hyperplasia; slight spongiosis; parakeratosis; and occasional lymphocytes in the lower half of the epidermis.[10] Within the superficial dermis is a bandlike or perivascular lymphohistiocytic infiltrate. Multinucleated giant cells are often noted within interstitial infiltrates along with rare to numerous eosinophils. Additional histologic findings include elastophagocytosis and lymphocytic emperipolesis by giant cells, necrobiosis, and necrotizing granulomatous vasculitis. Stains for elastic tissue show a complete absence of elastic fibers from the dermis. Occasionally, calcified elastic fibers are seen. The lymphocytes are predominantly of the helper T-cell phenotype and express CD4 and CD45RO. They may show loss or diminished expression of CD3, CD5, and/or CD7. Rare CD30-positive cells are identified. The giant cells express histiocytic markers. Many of the surrounding histiocytes can be labeled with CD1a, suggesting that they represent Langerhans cells or dermal dendritic cells.[12]

## Variants Not Listed Under the WHO/EORTC Classification

MF has been defined as a "dermatologic masquerader", and several clinical and/or histopathologic variants have been described.

*Bullous MF* is an extremely rare variant with an aggressive clinical course. Patients present with subcorneal, intraepidermal, or subepidermal blisters with negative immunofluorescence (direct and indirect). Direct cytotoxicity by neoplastic T-cells, decreased adhesion between basal keratinocytes and papillary dermis due to the confluence of Pautrier microabscesses, or extreme spongiosis within the epidermis are possible mechanisms.[40-43]

*Poikiloderma vasculare atrophicans* is a term applied to a spectrum of diseases ranging from a rare form of early MF to several inflammatory dermatoses. Histology reveals an atrophic epidermis with loss of rete ridges, an interface dermatitis with a superficial, band-like infiltrate of lymphocytes with epidermotropism, and a thickened papillary dermis. Necrotic keratinocytes and pigment incontinence may be a prominent finding. Dilated capillaries are present within the superficial dermis. This variant has also been referred to as the "lichenoid" type of MF.[3]

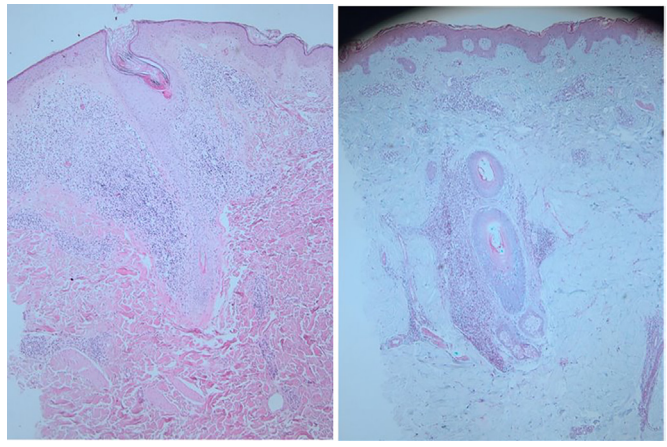

**Figure 11.** Follicular and perifollicular infiltrate of small to medium-sized lymphocytes and mucin accumulation in follicular epithelium with alcian blue dye

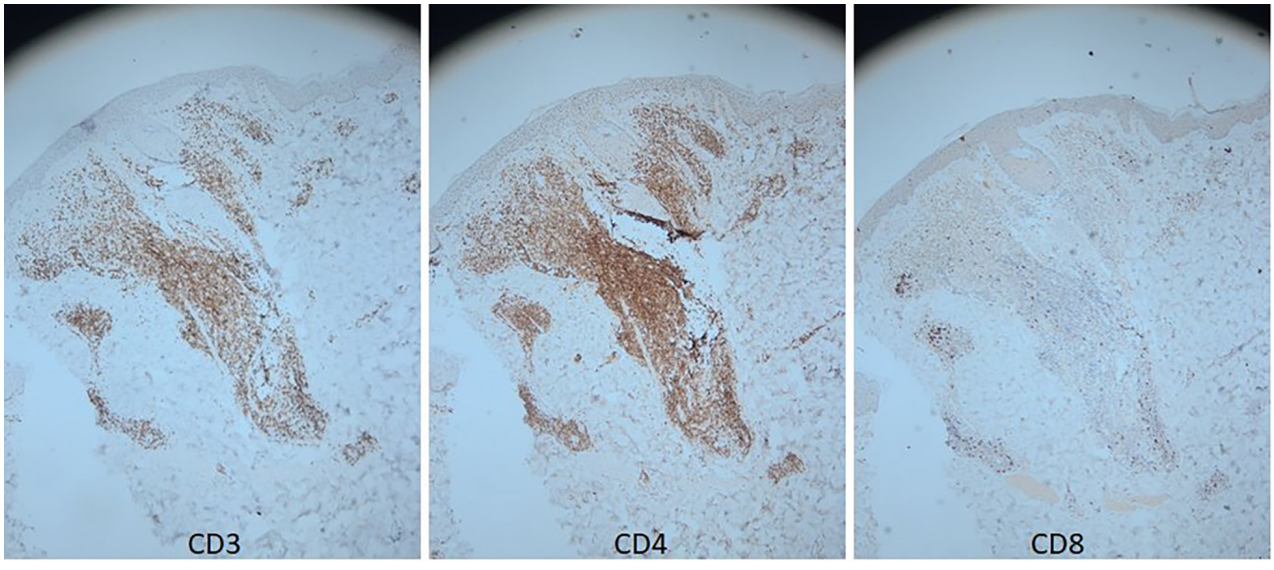


**Figure 12.** Folliculotropic mycosis fungoides with $CD3^+$, $CD4^+$, $CD8^-$ phenotype

*Papular MF* is a new clinical variant of early MF characterized by papules rather than conventional patches at the onset of disease. Histopathologic examination reveals conventional features of MF, but in tiny papules the infiltrate is restricted to a part only of the biopsy specimen.[3,44]

*Pustular MF* is a very rare form of the disease and is suggested to be associated with subcorneal neutrophil abscesses (i.e., true pustules) or to reflect conspicuous Pautrier microabscesses.[45,46]

*Erythrodermic MF* may develop during the course of disease. The histologic features of erythrodermic MF can be subtler than the features of patch and plaque stage MF, mostly due to lesser epidermotropism by neoplastic T-cells. Furthermore, findings of more parakeratosis, acanthosis, or papillary dermal fibrosis, along with prominent telangiectasia and increased mitotic figures, would be more commonly seen in erythrodermic than in patch stage MF.[47] Rarely, swelling of the lymph nodes and presence of circulating neoplastic cells ("Sézary cells") are observed as well, thus showing overlapping clinical features with Sézary syndrome. The histopathologic and phenotypic features are identical to those of conventional MF. However, patients with erythrodermic MF show more commonly a B0 or B1 blood involvement, whereas a B2 involvement is needed for the diagnosis of Sézary syndrome. Differentiation of erythrodermic MF from Sézary syndrome on histopathological grounds is usually not possible.[48]

*Hypopigmented MF* may observed more frequently in dark-skinned individuals and is one of the most frequent variants seen in children. The histopathologic findings are similar to classic MF, although lichenoid infiltrates are weaker, and fibroplasia is usually absent probably because of early patch stage presentation. $CD4^{-}CD8^{+}$ immunophenotype is more common in this variant. A reduced number of epidermal melanocytes suggest a melanocyte-targeted cytotoxicity by neoplastic $CD8^{+}$ T-cells as a possible pathomechanism. $CD4^{-}CD8^{+}$ immunophenotype is more common in this variant.[10]

*Hyperpigmented MF* is characterized by markedly hyperpigmented lesions, corresponding histopathologically to the presence of pigment incontinence and abundant melanophages in the papillary dermis. The phenotype of these lesions is more often cytotoxic than helper, possibly explaining the damage at the dermo-epidermal junction and subsequent pigment incontinence. Hyperpigmented MF may show some overlapping features with poikilodermatous MF, but in hyperpigmented MF the prominent telangiectasia and retiform pattern are missing clinically, and histopathologically there is no increase in superficial, telangiectatic vessels.[3] On immunohistochemical studies, epidermotropic T-cells exhibit a predominantly $CD8^{+}$ phenotype, although few $CD4^{-}CD8^{-}$ cases have also been reported.[10]

*Granulomatous MF* is an unusual histologic variant of the disease with granuloma formation. Epidermotropism may be a helpful clue to differentiate it from granulomatous dermatitis or tumors.[3]

Purpuric hue, seen in *purpuric MF*, corresponds to many extravasated erythrocytes and siderophages histopathologically. This variant of MF mimics the pigmented purpuric dermatoses both clinically and histopathologically.[49]

*Interstitial MF* is a variant of the disease that does not have a characteristic clinical presentation, but shows histopathologically a pattern that may be misinterpreted as that of an inflammatory dermatosis. Epidermotropism and a band-like pattern are usually missing, and histology shows dermal infiltrates of lymphocytes dissecting the collagen bundles. Immunohistology confirms that most interstitial cells are T-lymphocytes, which is a helpful clue for the differential diagnosis with interstitial inflammatory dermatoses.[3]

Ichthyosiform scaling is the only clinical manifestation of *ichthyosis-like MF*. Histologically, the features of ichthyosis (hyperkeratosis, acanthosis with a thinned granular cell layer) are superimposed upon MF.[50,51]

The *verrucous* presentation of MF is one of the many atypical forms of the disease and may be clinically mistaken for a halogenoderma, or deep fungal or atypical mycobacterial infection. Histologically, in addition to atypical, epidermotropic T-lymphocytes, verrucous, keratosis-like changes with epidermal acanthosis, papillomatosis, and parakeratosis may also be observed.[52]

*Invisible MF* is an exceedingly rare form of MF. It is characterized by neoplastic T-cell infiltrates in clinically normal-appearing skin. Pruritus without visible disease can be an associated finding, which is usually the trigger for the biopsy. The diagnostic criteria include findings of epidermotropic and superficial perivascular infiltrates of T-cells with immunophenotypic and molecular genetic evidence of clonality. Invisible MF can be seen either before or after the development of classic patches or plaques.[11]

Other very rare MF variants have been described that clinically mimic benign dermatoses. Many of these variants have been observed in anecdotal cases only. On the other hand, there are also benign dermatoses that show histopathological features similar to MF. Early morphea may be an example of atypical clonal intraepidermal lymphocytes indistinguishable from MF. Clinical course and typical histological dermal findings of morphea and no clinical features of MF at presentation or after a follow-up of up to 5 years may lead to the diagnosis of MF.[53]

All these variants above underline once again the protean clinicopathologic features of MF and the need for a high level

of suspicion when diagnosing cutaneous eruptions that do not fit well into a precise category of inflammatory skin disease.

## Conclusion

Other very rare MF variants have been described that clinically mimic benign dermatoses. Many of these variants have been observed in anecdotal cases only. On the other hand, they underline the protean clinicopathologic features of MF and the need for a high level of suspicion when diagnosing cutaneous eruptions that do not align with a precise category of inflammatory skin disease.

### Footnotes

**Financial Disclosure:** The author declared that this study received no financial support.

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Review

# The Role of Dermoscopy, Ultrasonography and Confocal Microscopy in the Diagnosis of Mycosis Fungoides: Literature Review

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## Abstract

Mycosis fungoides (MF), the most prevalent form of cutaneous T-cell lymphoma, is a chronic malignancy often challenging to diagnose in its early stages due to its overlapping clinical features with benign inflammatory dermatoses such as psoriasis, eczema, and atopic dermatitis. This chapter explores the roles of three non-invasive imaging techniques-dermoscopy, high-frequency ultrasound (HF-USG), and reflectance confocal microscopy (RCM)-in improving diagnostic accuracy, disease staging, and monitoring therapeutic responses in MF. Dermoscopy is instrumental in identifying characteristic vascular patterns and pigmentation that differentiate early-stage MF from other inflammatory conditions. HF-USG provides detailed imaging of the skin's internal architecture, with particular emphasis on the subepidermal low echogenic band, which serves as a key diagnostic marker of MF. Additionally, RCM offers near-histological visualization of cellular structures, enabling the detection of epidermotropic lymphocytes and Pautrier microabscesses, which are hallmark features of MF. The integration of these modalities significantly enhances diagnostic precision, reduces the need for invasive procedures, and offers a comprehensive framework for non-invasive evaluation of MF.

**Keywords:** Mycosis fungoides, dermatoscopy, confocal microscopy, ultrasonography, diagnosis

## Introduction

Mycosis fungoides (MF), the most prevalent form of cutaneous T-cell lymphoma (CTCL), is a chronic malignancy with clinical features characterized by early, subtle presentations that may mimic benign inflammatory conditions like psoriasis, eczema, and atopic dermatitis These overlaps, particularly in the early stages, pose challenges for accurate diagnosis.[1]

Traditional methods of diagnosis, such as clinical inspection, histopathology, and immunohistochemistry are invaluable but often invasive and prone to variability, particularly in early-stage MF, where clinical and histopathologic signs can be subtle.[2]

To overcome these challenges, advanced non-invasive diagnostic modalities such as dermoscopy, high-frequency ultrasound (HF-USG), and reflectance confocal microscopy (RCM) have become integral in improving diagnostic precision.

This review focuses on the utility of these imaging tools in detecting, staging, and monitoring MF, emphasizing their non-invasive nature and their ability to complement traditional histopathological methods.

### Dermoscopy in Mycosis Fungoides Diagnosis

Dermoscopy is a well-established technique in dermatology for the evaluation of skin lesions, offering a non-invasive

**Submission:** 20-Oct-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 27-Nov-2024

Access this article online

Quick Response Code:

**Website:** www.turkjdermatol.com

**DOI:** 10.4274/tjd.galenos.2024.83007

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**How to cite this article:** Tatlıparmak A. The role of dermoscopy, ultrasonography and confocal microscopy in the diagnosis of mycosis fungoides: literature review. Turk J Dermatol. 2025;19(1):36-40.

 

method to observe vascular patterns, pigmentation, and scaling at a magnified level. In MF, dermoscopy provides valuable insights into the morphology of early lesions, which often present diagnostic challenges when assessed through clinical examination alone.[3]

**Key dermoscopic features:** Plaque stage: More advanced lesions, such as those seen in the plaque stage of MF, demonstrate dotted vessels and white patches (Figure 1a). These are particularly evident in thicker, more infiltrated lesions, where dermoscopic features become more pronounced.[4,5]

**Vascular patterns in early-stage mycosis fungoides:** One of the most distinguishing dermoscopic features of early MF is the presence of fine, short linear vessels arranged in a serpentine or spermatozoon-like pattern (Figure 1b). These vessels are usually accompanied by orange-yellowish patchy areas, which represent lymphocytic infiltration and the breakdown of blood by-products, such as hemosiderin. The vascular morphology in MF is often irregular and scattered, reflecting the patchy nature of lymphocytic infiltration in the superficial dermis.[4,5]

Dermoscopic vascular patterns in MF are distinct from other papulosquamous conditions. For instance, the dotted and linear vessels seen in MF are significantly different from the dilated capillaries observed in psoriasis and the irregular capillaries found in chronic eczema. In MF, vessels often run vertically along the dermal papillae and horizontally in the subpapillary dermis.[6,7]

**Scaling and surface features:** In early MF, fine white scaling is often present, but it tends to be thin and perifollicular, forming around hair follicles rather than covering the entire lesion (Figure 1). This perifollicular pattern contrasts with the thicker and more diffuse scaling seen in psoriasis, where scaling is more widespread and associated with hyperkeratosis. In psoriasis, the scaling tends to be silvery-white and covers a larger portion of the plaque surface.[7,8]

Recent studies indicate that certain hair shaft abnormalities, including multiple pili torti (observed in 67% of MF cases), 8-shaped hairs, and rapidly tapered hair shafts, are predominantly associated with MF. In contrast, single pili torti appear infrequently in psoriasis (16%) and eczematous dermatitis (8%), suggesting that these findings can aid in distinguishing MF from other inflammatory skin conditions.[9]

**Dermoscopic-histopathologic correlation:** Dermoscopy findings in MF correlate closely with histopathologic features. Fine, short linear vessels correspond to dermal capillaries within the papillary dermis, infiltrated by atypical T-lymphocytes. Additionally, orange-yellowish patches seen in dermoscopy reflect hemosiderin deposits or dense inflammatory infiltrates, aiding in the differentiation from other dermatoses (Figure 1a).[8]

Dermoscopic findings exhibit notable variation across different clinical types of MF, with each subtype showing specific patterns. In syringotropic MF, for instance, characteristic dermoscopic features include follicular accentuation, plugging, and bluish areas that correlate with eccrine gland involvement. Conversely, folliculotropic MF often presents with follicular obliteration without the bluish hue observed in syringotropic MF. These distinct dermoscopic patterns reflect underlying histopathologic differences between MF subtypes, underscoring dermoscopy's utility in accurately differentiating and diagnosing these variants.[10]

Additionally, purpuric dots are sometimes visible in early-stage MF, corresponding to extravasation of red blood cells due to inflammation-induced vascular damage. These purpuric dots are rarely seen in other inflammatory conditions and can serve as a differentiating feature.[10]

## Summary Highlights of the Dermoscopic Findings That Differentiate Other Inflammatory Dermatoses from Mycosis Fungoides

### Psoriasis (plaque psoriasis):

- **Vessels:** Regular dotted vessels throughout the lesion, representing dilated capillaries within dermal papillae.
- **Scaling:** Thick silvery-white scaling covering most of the plaque.
- **Pigmentation:** Homogeneous pink to red background, with no orange-yellow areas.
- **Conclusion:** The uniformity of vascular patterns and diffuse scaling in psoriasis differ from the irregular, fine linear vessels and localized perifollicular scaling seen in MF.[2]

### Chronic eczema:

- **Vessels:** Dotted vessels similar to psoriasis but more widely spaced and less uniform.

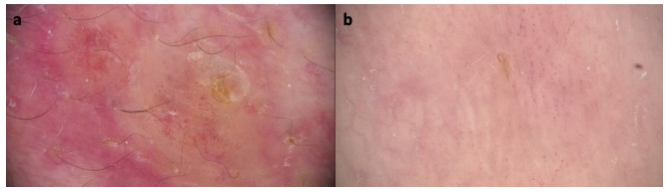


**Figure 1.** (a) White scale and orange-yellowish pathces. (b) Spermatozoon-like vascular pattern

- **Scaling:** More diffuse scaling, although not as thick as psoriasis.

- **Pigmentation:** Lesions typically exhibit a homogeneous red background with less color variation.

- **Conclusion:** The lack of orange-yellowish areas and less serpentine vascular patterns distinguish chronic eczema from early-stage MF.[2,3]

### Atopic dermatitis:

- **Vessels:** Exhibits dotted vessels, but usually within areas of lichenification and xerosis.

- **Scaling:** Tends to show dry scaling associated with lichenification, unlike the fine white perifollicular scaling in MF.

- **Pigmentation:** Often presents with a pale pink background, with little evidence of orange-yellowish pigmentation.

- **Conclusion:** Atopic dermatitis lacks the characteristic vascular features and orange-yellowish patches seen in early-stage MF.[2,3]

In conclusion, the presence of fine, short linear vessels, orange-yellowish patchy areas, and perifollicular white scaling are distinctive markers of early MF. Recognizing these dermoscopic hallmarks is essential for clinicians to improve diagnostic accuracy and initiate appropriate treatment at an earlier stage, potentially altering the disease course and improving patient outcomes.

## High-Frequency Ultrasound in Mycosis Fungoides Diagnosis

HF-USG is a pivotal imaging modality for evaluating the structural and morphological changes in MF lesions. Unlike dermoscopy, which primarily assesses surface characteristics, HF-USG provides a detailed view of the skin's internal architecture, including the epidermis, dermis, and subcutaneous layers.[11]

HF-USG uses sound waves to produce detailed images of the skin's structural layers. It is a non-invasive imaging modality that has proven valuable in dermatological practice, particularly for measuring skin thickness and assessing the depth of infiltration in various cutaneous conditions.[12]

HF-USG operates at frequencies typically between 20 MHz and 50 MHz, which allows for high-resolution imaging of superficial structures like the epidermis, dermis, and upper subcutaneous tissue.[11] The depth of penetration of HF-USG is inversely proportional to its frequency, meaning higher frequencies provide more detailed images but can only assess superficial layers up to 15-25 mm.[11,12]

The ultrasound image is generated based on the reflection of sound waves from tissues of different densities. As the ultrasound waves encounter boundaries between different tissues (e.g., the epidermis and dermis), they are reflected back to the transducer. The intensity and timing of these reflections are translated into an image based on the echogenicity (brightness) of the tissues.[11]

**Subepidermal low echogenic band:** The presence of the subepidermal low echogenic band (SLEB) is one of the hallmark ultrasound findings in MF (Figure 2). This band represents the infiltration of atypical T-cells in the superficial dermis and is a key differentiator between MF and other inflammatory dermatoses.[13]

The SLEB is typically seen as a hypoechoic (dark) band located just below the epidermis. In MF, this band is significantly thicker compared to inflammatory conditions like psoriasis and eczema. The thickness of the SLEB correlates with the degree of infiltration of malignant cells in the dermis and can serve as a reliable diagnostic marker.[14]

In comparison to other dermatoses, the SLEB in MF is more prominent and persists even in patch-stage lesions, where other inflammatory conditions may show a thinner or absent SLEB.[15]

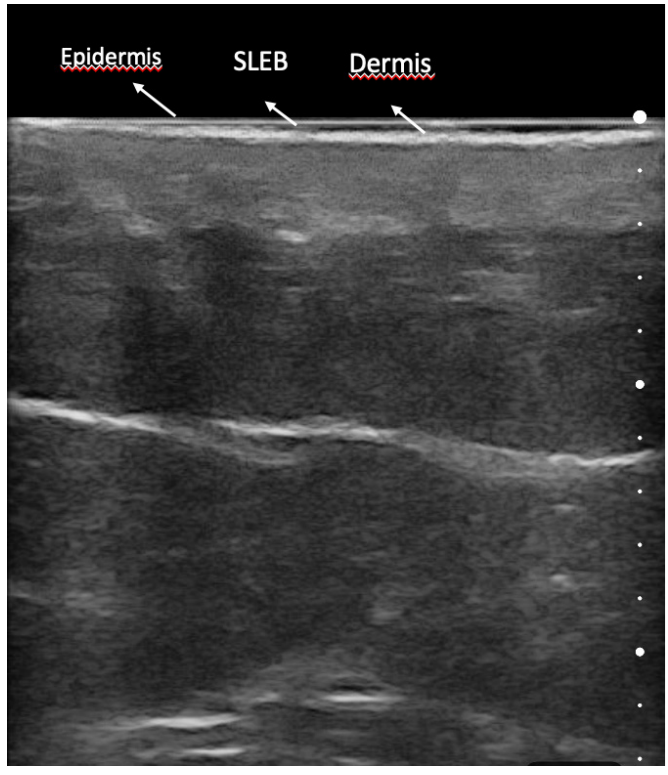


**Figure 2.** SLEB in MF lesion
*SLEB: Subepidermal low echogenic band, MF: Mycosis fungoides*

**Epidermal and dermal changes:** HF-USG can assess the thickness and echogenicity of the epidermis and dermis. In MF, there is a reduction in dermal echogenicity, which reflects the presence of atypical lymphocytes infiltrating the skin. This reduction is due to the displacement of normal collagen and dermal structures by the infiltrating cells, resulting in decreased reflection of the ultrasound waves.[16]

In addition to the decreased echogenicity, MF lesions often show increased epidermal thickness**,** particularly in plaque-stage MF. This thickening is a result of epidermal hyperplasia and infiltration by malignant cells, which can be clearly visualized in HF-USG.[16]

**Vascular involvement:** HF-USG is also capable of detecting changes in the vascular structures of the skin. In MF, increased blood flow to the affected area, as well as dilated blood vessels, can be identified using color Doppler ultrasound, which is an adjunct to HF-USG. These vascular changes often correlate with the inflammatory nature of the lesions and the presence of malignant infiltrates within the skin.[17]

Unlike psoriasis, which often shows prominent vascular changes related to dilated capillaries in dermal papillae, the vascular alterations in MF tend to be less uniform and may reflect localized areas of lymphocytic infiltration.[14,18]

**Clinical utility of HF-USG:** HF-USG is an helpfull tool for distinguishing between patch and plaque stages of MF. In patch-stage MF, HF-USG shows superficial dermal involvement with minimal deep tissue changes. In contrast, plaque-stage lesions exhibit deeper infiltration into the dermis, which can be quantitatively measured using HF-USG. The SLEB observed in HF-US is not exclusive to MF or Sézary syndrome (SS), thus limiting the diagnostic specificity of HF-US for these conditions. Consequently, while HF-US provides valuable structural and staging insights, its diagnostic value remains relatively restricted in distinguishing MF/SS from other dermatoses.[17]

HF-USG has demonstrated effectiveness in monitoring treatment response in MF patients undergoing PUVA and UVA1 phototherapy. The SLEB was present in all patients prior to treatment. After phototherapy, significant thinning or complete disappearance of the SLEB was observed, correlating with clinical improvement. In cases of complete response, the SLEB vanished entirely, while in cases of partial response, there was a reduction in SLEB thickness. These findings indicate that HF-USG can serve as an objective, non-invasive tool to evaluate the efficacy of MF treatments by quantifying changes in SLEB thickness and dermal echogenicity, which correspond to treatment outcomes.[19]

### Reflectance Confocal Microscopy in MF Diagnosis

RCM offers a high-resolution, cellular-level view of the epidermis and superficial dermis, providing a near-histological assessment without the need for biopsy. RCM allows real-time imaging, which is particularly useful in early-stage MF where histopathologic features may be subtle.[20]

In early-stage MF, RCM typically reveals epidermotropic lymphocytes, which appear as round, refractile cells scattered within the epidermis.[21] This corresponds to the histological finding of atypical T-cells invading the epidermis.[22]

In some cases, RCM can detect spongiosis, characterized by intercellular edema, which correlates with early MF histology.[22,23]

More advanced lesions in plaque-stage MF may show Pautrier microabscesses, which appear as vesicle-like structures filled with refractile material. These are considered diagnostic of MF and can be visualized using RCM.[24]

**Limitations of RCM:** Despite its advantages, RCM has some limitations, including limited imaging depth (typically up to 200-300 microns), which makes it less effective for evaluating deeper dermal involvement. Moreover, RCM may struggle to distinguish between certain cell types, particularly in the context of complex inflammatory infiltrates.[25]

RCM is a valuable adjunct to traditional histopathology. It is particularly useful for selecting optimal biopsy sites, reducing false-negative biopsy results, and providing additional information in ambiguous cases.[22]

## Conclusion

The integration of dermoscopy, HF-USG and RCM offers a robust, non-invasive diagnostic framework for MF. Each modality provides unique insights that, when combined, significantly enhance diagnostic accuracy.

- Dermoscopy provides detailed surface-level information on vascular patterns, scaling and pigmentation.

- HF-USG adds depth by evaluating lesion infiltration, SLEB thickness, and dermal changes.

- RCM offers near-histologic resolution of epidermal and dermal structures, identifying atypical lymphocytes, microabscesses, and other key features.

### Footnotes

**Financial Disclosure:** The author declared that this study received no financial support.

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Review

# Treatment Algorithms for Mycosis Fungoides and Sézary Syndrome

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## Abstract

Mycosis fungoides (MF) is the most prevalent form of cutaneous T-cell lymphoma (CTCL). Tumor, lymph nodes, metastasis, and blood (TNMB) staging serves as the primary prognostic factor that significantly influences treatment strategies. The objectives of MF therapy are tailored to each patient, focusing on achieving adequate responses to alleviate symptoms and reducing the risk of progression. Continuing or maintenance therapies with low adverse effects are preferred to sustain disease control and enhance quality of life. This review is based on the latest international treatment guidelines from the European Organization for Research and Treatment of Cancer (EORTC), the National Comprehensive Cancer Network, and the British Association of Dermatologists in the United Kingdom Cutaneous Lymphoma Group. In early-stage MF, skin-directed treatments are effective, whereas systemic agents are required for early-stage refractory MF and advanced cases, including Sézary syndrome (SS). Biological and targeted therapies, as well as immunosuppressive treatments, are utilized in more severe cases, with new therapies for advanced disease currently under investigation in clinical trials. This review provides a comprehensive overview of the current treatment options for MF/SS by examining their mechanisms of action, efficacy, and side effects, thereby guiding clinicians in optimizing patient care.

**Keywords:** Cutaneous lymphoma, mycosis fungoides, Sézary syndrome, T-cell lymphoma, treatment

## Introduction

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma (CTCL), and many clinicopathologic variants of MF have been described. Tumor, lymph nodes, metastasis, blood (TNMB) staging remains the most important prognostic factor in CTCL, forming the basis of the treatment approach. In addition to clinical stage, histological evidence of folliculotropic and large cell transformation can be associated with poorer prognosis, which may warrant more aggressive treatment. The objectives of MF therapy should be tailored to the individual patient, but frequently include achieving an adequate response to reduce and control symptoms and minimize the risk of progression. Therapies with a low incidence of adverse effects and an absence of cumulative toxicity are frequently administered on an ongoing or maintenance basis to enhance and sustain disease control and quality of life.[1]

In CTCL, the decision to continue or modify treatment is based on clinical observations. Relapsed diseases may respond to prior therapies. Unlike other non-Hodgkin lymphomas, treatment responses can differ across compartments (skin, blood, lymph nodes), necessitating careful consideration in advanced-stage patients. The treatment of MF/Sézary syndrome (SS) requires a multidisciplinary approach involving dermatology, hematology, medical oncology, and radiation oncology. In patients with early-stage disease, skin-directed treatments

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**Submission:** 30-Sep-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 19-Oct-2024

Access this article online

Quick Response Code:

Website: www.turkjdermatol.com

DOI: 10.4274/tjd.galenos.2024.60362



**How to cite this article:** Şanlı H, Erol Mart HM. Treatment algorithms for mycosis fungoides and sézary syndrome. Turk J Dermatol. 2025;19(1):41-60.

(SDT) may be an effective option. However, patients with early-stage refractory MF or advanced MF and SS may require treatment with systemic agents. In this case, biological or targeted therapies, such as extracorporeal photochemotherapy, interferons (IFN), bexarotene, and histone deacetylase (HDAC) inhibitors, are employed as monotherapy or in combination with SDT. Immunosuppressive therapies, either as monotherapy (e.g., prelatrexate and methotrexate (MTX), gemcitabine, liposomal doxorubicin) or in combination with other chemotherapeutics, are employed in refractory or rapidly progressive cases with diffuse involvement, lymph node involvement, and/or metastasis. New treatments for advanced diseases are currently being developed through clinical trials. Patients with a resistant or progressive course should be enrolled in clinical trials at every stage of the disease.[2]

This review will provide an overview of the treatment options available for MF/SS, including an analysis of the mechanisms of action, efficacy, and side effects.

## Methods

The treatment algorithms were based on the international guidelines for the treatment of MF, namely the European Organization for Research and Treatment of Cancer (EORTC), 2023 (1); the National Comprehensive Cancer Network (NCCN), version 3.2024 (2); and the British Association of Dermatologists and the United Kingdom Cutaneous Lymphoma Group guidelines (BAD-UKCLG), 2018.[3] Common and divergent aspects of these guidelines have been subjected to detailed analysis and summary to facilitate treatment planning.

The text includes information about whether the treatments mentioned have received approval from the US. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Although not currently included in the guidelines, this review also addresses the nuances of treatment for clinicopathological MF variants and specific patient populations.

## Results

Accurate diagnosis and appropriate staging of patients with MF/SS are fundamental aspects in selecting the optimal therapeutic approach. MF and SS are both treatable, yet not curable, with conventional systemic therapy. The aforementioned principle does not apply to allogeneic stem cell transplantation (alloSCT) in cases of advanced disease and to a small number of patients with prolonged remission following SDT in localized early stages, where the primary objective of treatment is to achieve a cure.

Treatment of MF/SS should be performed in a stepwise and stage-adapted manner, with a primary focus on maintaining quality of life. In the absence of larger randomized controlled trials, the evidence base for decision making is limited. However, guidelines developed by various national and international groups can provide valuable assistance in this context. In general, the NCCN guidelines encompass a broader treatment spectrum, incorporating therapies that have shown benefits in small case series. In contrast, the EORTC guidelines focus on therapies approved in Europe that have more definitive evidence of efficacy.

The EORTC guidelines recommend that second-line options be reserved for patients who are refractory (showing no or only minimal response to treatment and experiencing progression during therapy) or who have contraindications to first-line treatment. In cases of relapse after successful first-line treatment, patients should not be considered refractory, and therapy can typically be reinitiated. The individual choice of appropriate therapy may vary according to clinical presentation and treatment availability (Table 1).[1]

The BAD-UKCLG guidelines recommend the establishment of supranetwork multidisciplinary teams (MDTs) that include dermatologists, clinical oncologists, hemato-oncologists, dermatopathologist, and hematopathologist. All patients with early-stage MF refractory to SDT and late-stage MF and SS should be reviewed by supranetwork MDTs to agree on a management plan and provide the opportunity for consideration in appropriate clinical trials. Additionally, the MDT is responsible for overseeing patients requiring specialized treatments, such as total skin electron beam therapy (TSEB), extracorporeal photopheresis (ECP), and stem cell transplantation (Figure 1).[3]

### Watch and Wait (Expectant Policy)

Patients with stage IA disease have a low risk of progression and a life expectancy comparable to that of the general population. Therefore, the "watch and wait" approach remains a valid option for these patients, particularly those classified as T1a (with patches covering < 10% of the body surface area). However, careful monitoring is essential because some patients will eventually progress; over a 10-year period, approximately 10% of patients with early-stage disease experience progression.[1] The expectant policy has been recommended by the EORTC, but it is not included in the NCCN and BAD-UKCLG guidelines.

### Skin-Directed Treatment

SDT is a recommended first-line intervention in the early stages of MF. In advanced stages, they may also be used in

combination with systemic options to control symptoms such as pain and pruritus and to improve skin tumor burden.

## Topical Therapies

Topical therapies have demonstrated clinical efficacy for patches and thin plaques; however, the paucity of well-controlled studies limits the quality of evidence. A significant proportion of topical therapies have not been granted a license for use in MF.

Topical corticosteroids, nitrogen mustard, topical retinoids, carmustine, imiquimod, and topical calcineurin inhibitors (TCI) are discussed in detail in the context of topical therapies. However, topical MTX, 5-fluorouracil, and peldesine (a potent, competitive, reversible, and orally active purine nucleoside phosphorylase inhibitor) are not included in any of the three guidelines.

**Table 1. EORTC recommendations according to clinical stage[1]**

| | |
|---|---|
| **Recommendations for the treatment of MF stages IA, IB, and IIA** | |
| **First-line** | **Second-line** |
| Expectant policy (mainly T1a)<br>SDT<br>- Topical corticosteroids (mainly T1a and T2a)<br>- Topical chlormethine<br>- nbUVB (mainly T1a and T2a)<br>- PUVA<br>- Localized RT (for localized MF including pagetoid reticulosis) | Systemic therapies<br>- Retinoids<br>- IFN-α<br>TSEB (mainly T2b)<br>Brentuximab vedotin<br>Mogamulizumab<br>Low-dose MTX |
| **Recommendations for treatment of MF stage IIB** | |
| **First-line** | **Second-line** |
| Systemic therapies<br>- Retinoids<br>- IFN-α<br>TSEB<br>Brentuximab vedotin<br>Mogamulizumab<br>Monochemotherapy (pegylated liposomal doxorubicin, gemcitabine)<br>Low-dose MTX<br>Localized RT | (Poly-)chemotherapy<br>Brentuximab vedotin<br>Mogamulizumab<br>AlloSCT |
| **Recommendations for the treatment of MF stages IIIA and IIIB** | |
| **First-line** | **Second-line** |
| Systemic therapies<br>- Retinoids<br>- IFN-α<br>ECP<br>Brentuximab vedotin<br>Mogamulizumab<br>Low-dose MTX<br>TSEB | Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)<br>Brentuximab vedotin<br>Mogamulizumab<br>AlloSCT |
| **Recommendations for the treatment of MF stages IVA and IVB** | |
| Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)<br>Radiotherapy (TSEB and localized)<br>Brentuximab vedotin<br>Mogamulizumab<br>Alemtuzumab (mainly in B2)<br>AlloSCT | |
| **Recommendations for the treatment of SS** | |
| **First-line** | **Second-line** |
| ECP<br>Systemic therapies in combination with ECP or PUVA<br>- Retinoids<br>- IFN-α<br>Chlorambucil + prednisone<br>Low-dose MTX | Mogamulizumab<br>Brentuximab vedotin<br>Alemtuzumab<br>Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)<br>AlloSCT |

AlloSCT: Allogeneic stem cell transplantation, CHOP: Cyclophosphamide doxorubicin vincristin prednisone, ECP: Extracorporeal photopheresis, IFN-α: Interferon alpha, MF: Mycosis fungoides, MTX: Methotrexate, nbUVB: Narrowband ultraviolet-B, PUVA: Psoralen plus ultraviolet-A, RT: Radiotherapy, SDT: Skin-directed treatment, SS: Sézary syndrome, TSEB: Total skin electron beam therapy, *For stage IV disease, no distinction is made between first- and second-line options because of insufficient evidence to justify such separation

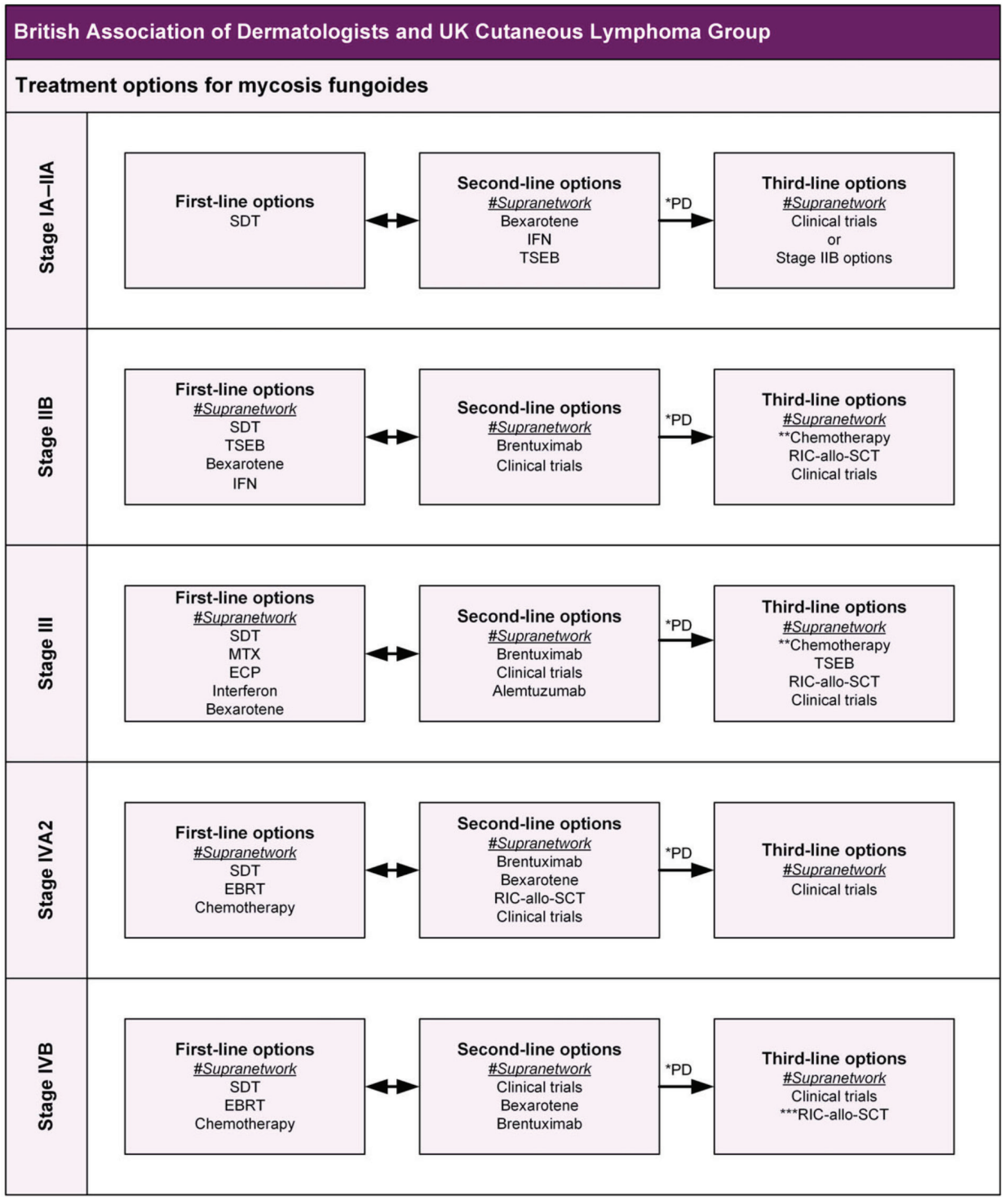


**Figure 1.** British Association of Dermatologists and the United Kingdom Cutaneous Lymphoma Group guidelines for the treatment of mycosis fungoides.[3] *EBRT: External beam radiotherapy with photons or electrons for lymph node, soft tissue or visceral lymphoma, ECP: Extracorporeal photopheresis, IFN: Interferon, MTX: Methotrexate, PD: Progressive disease, RIC-allo-SCT: Reduced intensity allogeneic stem cell transplantation, SDT: Skin-directed therapy (topical steroids, ultraviolet B, psoralen-ultraviolet A, skin radiotherapy, topical nitrogen mustard), TSEB: Total skin electron beam radiotherapy. Skin radiotherapy indicates superficial radiotherapy or EBRT to skin patches, plaques and tumours. #Supranetwork: refers to the supranetwork multidisciplinary team (MDT) meeting for treatment decision. *PD and exhausted first- and second-line options. **Chemotherapy as recommended by the supranetwork MDT. ***Consider only if the patient has durable complete response. ↔ indicates that after treatment, patients may respond to treatments included in earlier "line" options. Patients can move between first- and second-line options.*

## Topical Corticosteroids

Topical corticosteroids induce lymphocyte apoptosis and inhibit the adhesion of lymphocytes to endothelial and intracellular areas. Since the early 1960s, these agents have been widely used in the treatment of MF owing to their accessibility, ease of application, and minimal adverse effects. However, the efficacy of these agents in the treatment of MF remains inconclusively supported by experimental evidence.[1]

In 2003, Zackheim[4] employed high-potency, class I topical steroids (predominantly clobetasol) as a primary therapeutic modality in approximately 200 patients with patch and early plaque stage MF and documented overall response rates (ORR) exceeding 90% in stage T1 patients and over 80% in stage T2 patients. They reported that contrary to the recommendations for the use of topical corticosteroids (maximum dosage of 50 g/week for two consecutive weeks, with careful application in sensitive areas such as the face, axilla, and groin), applying them without regard to the total dose and using occlusion in intertriginous areas, as well as in widespread body lesions, is an effective treatment for early-stage MF. It is noteworthy that cutaneous side effects (such as purpura, atrophy, and striae) that would necessitate the discontinuation of treatment are rare. Furthermore, they suggested that individuals using high-dose topical corticosteroids for an extended period do not routinely need to be tested for adrenal insufficiency unless significant clinical findings are present.[4]

In a recent single-center retrospective study, Kartan et al.[5] confirmed the efficacy and safety of topical clobetasol propionate monotherapy in 37 patients with MF, demonstrating a high response rate (81%) in early-stage MF (stages IA/IB).

All three guidelines recommend the use of topical corticosteroids for the treatment of MF.

## Topical Chlormethine/Mechlorethamine (Nitrogen Mustard)

Mechlorethamine is an alkylating agent that impedes the processes of DNA replication and RNA transcription by forming crosslinks in DNA strands, ultimately resulting in apoptosis. There are solution, ointment, and gel formulations. In a randomized, controlled, multicenter trial involving 260 patients, the gel preparation demonstrated non-inferiority to the ointment, with response rates of 58.5% (gel) and 47.7% (ointment).[6]

The 0.016% gel preparation was approved by the FDA in 2013 for the topical treatment of stage IA and IB MF in patients who have received prior SDT. Subsequently, in 2017, the EMA granted it a broader indication for the topical treatment of MF in adult patients.[1]

The product should be applied once daily to all affected skin areas. Widespread disease can be applied to the whole body and safely. No evidence of systemic absorption after topical application was found, and no systemic toxicity was observed.[7] The side effect of contact dermatitis, which occurs in approximately 50% of patients, can be managed by treatment interruption and reintroduction with longer intervals between applications and by combination therapy with topical corticosteroids.[8] All three guidelines recommend the use of topical mechlorethamine for the treatment of early-stage MF.

## Topical Retinoids

Bexarotene is a retinoid X receptor (RXR) antagonist. The gel formulation has been approved by the FDA for topical treatment of cutaneous lesions in patients with CTCL (stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies.

In the phase I-II trial involving 67 patients with early-stage MF, the ORR was 63%, with 21% achieving complete response (CR). The estimated median response duration from the start of therapy was 99 weeks. Patients who had not received prior therapy for MF had a higher response rate (75%) than those who had previously undergone topical treatments (67%).[9]

In a phase III multicenter study involving 50 patients with early-stage refractory MF treated with topical bexarotene gel 1%, the ORR was 44%, with a complete remission rate of 8%. The most common adverse events (AE) likely associated with the drug were mild to moderate irritant dermatitis, pruritus and pain (primarily burning at the application site).[10]

A case report describes a patient with folliculotropic mycosis fungoides (FMF) who was refractory to intralesional and subcutaneous IFN-α-2a but achieved successful treatment with topical bexarotene gel, resulting in complete remission by the fifth month. This suggests that bexarotene gel is an effective option for localized early-stage FMF, even in cases resistant to systemic therapies.[11]

Bexarotene gel is not licensed in Europe. Thus, the current EORTC guidelines do not include any recommendations regarding the use of bexarotene gel.

Tazarotene, another topical retinoid, exerts antiproliferative and anti-inflammatory effects on the skin by binding to retinoic acid receptors (RAR)-β and RAR-γ. The efficacy and safety of tazarotene 0.1% topical gel/cream have been demonstrated in two small trials involving patients with early patch or plaque MF lesions.[12,13] Nevertheless, these results have not been followed up, the product has been discontinued in Europe, and it is not included as a treatment option in the current EORTC guideline.

## Topical Carmustine (BCNU)

Carmustine is an alkylating agent that forms DNA crosslinks, leading to apoptosis.

Topical carmustine is an effective treatment for early-stage MF, with high response rates of 92% and 64% observed in patients with T1 and T2 disease, respectively, at 36 months. However, greater absorption increases the risk of bone marrow suppression, thereby making the use of topical carmustine in maintenance therapy inadvisable. In contrast, the incidence of irritant contact dermatitis is lower (10%) than that of topical mechlorethamine.[14] Topical carmustine has been recommended by the NCCN (category 2B) guidelines, but it is not included in the EORTC guidelines.

## Topical Imiquimod

The toll-like receptor agonist imiquimod induces the production of local IFN-α, tumor necrosis factor-α, interleukin-1 (IL-1), and IL-6 and suppresses anti-apoptotic BCL-2. It is efficacious in a limited number of patients with early-stage MF refractory to other therapies.[15,16] Shipman and Scarisbrick[17] reported a total response rate of 80%, with a CR rate of 45%, and a partial response rate of 35% in 20 patients with stage IA-IIB MF treated with 5% imiquimod. The duration of topical imiquimod use among patients varied from 3 weeks to 7 months, employing different protocols, including application three nights a week or daily use. Although rare, some patients experience flu-like symptoms and fatigue; the side effects were primarily localized to the skin, and commonly include pain, erythema, local irritation, ulceration, and pruritus.[17]

Imiquimod may be used for areas with few lesions that are unresponsive to treatment or those located on sun-damaged skin, such as the forearms, scalp, and face.[2]

Topical imiquimod is recommended under the SDT section of the NCCN guidelines for patients with limited or localized skin involvement. Additionally, the EORTC and BAD-UKCLG guidelines include brief statements in case reports suggesting the potential benefit of imiquimod in the treatment of MF.

## Topical Calcineurin Inhibitors

In a phase II multicenter study of 39 patients with stage IA-IIA MF, topical pimecrolimus (1% cream) resulted in an ORR of 56% (one CR, 21 partial responses). It was well tolerated, and no patient required dose reduction or treatment discontinuation due to drug-related toxicity.[18] There is only one case report of the successful use of 0.1% tacrolimus ointment for the treatment of MF.[19] The NCCN guidelines suggest that TCI should be considered as a steroid-sparing treatment for perioral and periorbital lesions in patients with early-stage MF.[2] In contrast, the EORTC guidelines acknowledge that while the results are promising, they should be interpreted with caution, and no recommendation can currently be made regarding the use of TCI in MF.[1]

## Phototherapy

Psoralen plus ultraviolet-A (PUVA) and narrowband UVB (nbUVB) have a longstanding history in the treatment of MF and continue to be a mainstay in disease management, with high response rates in early-stage disease. Although some retrospective studies have indicated that PUVA is associated with superior outcomes and longer relapse-free intervals,[20] other studies have shown that UVB is as efficacious as PUVA for the management of early-stage MF.[21] However, these approaches have not been compared in randomized clinical trials.

A limited number of case series have demonstrated the efficacy of UVA1 phototherapy and excimer laser in the treatment of MF. However, only PUVA and nbUVB were considered in the EORTC guideline given that only these therapies have a sufficient body of evidence together with broad accessibility is available.[1]

## Psoralen-Ultraviolet A Photochemotherapy

A substantial body of evidence from extensive, non-randomized and retrospective case studies has demonstrated that PUVA is an effective treatment option for patients with early-stage disease, with high rates of CR.[3]

A retrospective study of long-term outcomes following complete remission from PUVA monotherapy reported that 30-50% of patients exhibited durable remission (10-year disease-free survival), but maintenance PUVA was given to almost all responding patients. One-third of patients presented with chronic photodamage and secondary skin cancers.[22]

The potential risks and benefits of phototherapy should be carefully considered in patients with a history of immunosuppressive medication use, basal cell carcinoma, squamous cell carcinoma, or melanoma.[2]

In cases where clinical necessity arises, a combination of phototherapy with systemic treatments (most commonly retinoids or IFN-α) may be considered.[1]

A study assessing the efficacy of PUVA and low-dose IFN-α-2a combination therapy in 68 patients with both early and advanced MF found that CR was achieved in 45.6% of patients, resulting in an ORR of 60.3%. The authors reported that CR was significantly higher in early-stage patients. However,

despite achieving CR, 80% of the patients experienced relapse, and no significant difference in disease-free survival was observed between early and advanced stages.[23]

The combination of PUVA and acitretin has been demonstrated to result in a reduction in the cumulative UVA dose required to achieve the best response, while exhibiting no difference in response rates when compared with PUVA alone. The duration of remission was found to be prolonged when retinoids were administered as maintenance therapy.[24]

The combination of PUVA and bexarotene is also safe, with similar response rates and durations to those observed with PUVA alone.[25]

The results of a prospective cohort study indicate that maintenance therapy does not prevent future relapse.[26] For maintenance PUVA, the risks may outweigh the benefits.

The pivotal questions regarding the impact of PUVA on progression and disease-specific survival remain unresolved.[3]

## Ultraviolet-B Phototherapy

The BAD-UKCLG guideline asserted that both nbUVB and broadband UVB (bbUVB) phototherapy can result in high CR rates, with a greater likelihood of responses in patients who have only patches.[3] However, the EORTC guidelines do not recommend bbUVB because of its disadvantages compared with nbUVB.[1]

NbUVB has antiproliferative, anti-inflammatory, and immunosuppressive properties. Some studies have demonstrated that nbUVB is as efficacious as PUVA for the management of early-stage MF, as previously mentioned. Additionally, a pediatric case series revealed high response rates (> 80%), including a number of CR in children with the hypopigmented variant of MF.[27]

Compared with PUVA, it has several significant advantages, including a lower risk of photocarcinogenesis, suitability for use in pregnant women and children, absence of gastrointestinal, hepatic, and other side effects associated with psoralene, and no need for eye protection after treatment. Maintenance treatment with nbUVB is still controversial.

## Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment option for solitary plaques that do not respond to topical treatment. The efficacy of MF treatment has been demonstrated in numerous case studies, as recently reviewed by Hooper et al.[28] CR was achieved in 67.3%, partial response in 13.5%, and no response in 3.8% of all included cases. The mean number of treatments in this analysis was 9.5, indicating that serial PDT is likely necessary for the successful treatment of MF.[28]

Further trials are necessary to optimize PDT protocols in terms of lesion type, thickness, and location. In addition, PDT is not a viable option for the treatment of large areas of the body surface or total skin exposure. Consequently, the EORTC and NCCN guidelines do not recommend the use of PDT for the treatment of MF.

## Radiation Therapy

MF is a highly radiosensitive malignancy, and localized radiotherapy represents an efficacious treatment option for patients at all stages of the disease. Photons and electrons can be used, and the dose ranges from 0.7 to 35 Gy.[1]

Local radiation therapy (RT) alone (without adjuvant therapy) has an ORR of 97-100% for unilateral or stage IA MF.[2,29]

In a study involving 31 patients with MF, the CR rate was 30% when low-dose RT (4 Gy in 2 fractions) was used, whereas increasing the dose to 8 Gy in two fractions yielded a CR rate of 92%. Patients who did not respond to low-dose RT were re-treated with 20 Gy administered in eight fractions. The study also concluded that higher radiation doses during disease progression are safe and feasible.[30]

The optimal management of individual plaque and tumor lesions is with external beam radiotherapy (EBRT), typically administered at a dose of 8-12 Gy. An 8 Gy dose may be given in a single fraction, whereas 24-30 Gy is recommended for achieving a more durable response or for unilateral presentations.[31]

Localized, peripheral nodal disease and visceral metastases can also be treated with EBRT. Central nervous system disease in patients with MF has a very poor prognosis. In patients who are suitable for treatment and have good performance status, palliative low-dose whole-brain RT may be an option.[3] Combinations of RT with other SDT and systemic therapies are possible.

## Total Skin Electron Beam Therapy

TSEB has a long history of treating MF. Conventional-dose (30-36 Gy) or low dose (< 30 Gy) TSEBT, either alone or in combination with adjuvant therapy, has been shown to be effective for all stages. To minimize the dose-dependent toxicity of TSEB, including erythema, desquamation, anhydrosis, alopecia, and xerosis, low-dose regimens (8-12 Gy) have been increasingly reported.

In a retrospective study that evaluated low-dose TSEBT in 102 patients with T2-T4 disease (excluding those with extracutaneous involvement), the ORRs were 98% and 97% for TSEBT doses of 10 Gy to less than 20 Gy and 20 Gy to less than 30 Gy, respectively. The overall survival (OS) and progression-free survival (PFS) rates were not significantly different between dose groups and were comparable to those observed with standard-dose TSEBT (≥ 30 Gy).[32] In a prospective study conducted in the UK, 103 patients received a low-dose TSEB schedule of 12 Gy administered in 8 fractions over a 2-week period. Of these patients, 54 had stage IB disease, 33 had stage IIB, 12 had stage III, and 4 had stage IV. The ORR was 87% (18% CR and 69% partial response). The median response duration was 11.8 months, and the median time to relapse after CR was 7.3 months. The treatment was well tolerated with lower toxicity than higher-dose schedules.[33]

It is common practice to follow TSEBT with systemic therapies, such as IFN or bexarotene, to maintain response in patients with stage IB-IIA disease and higher skin disease burden. Adjuvant systemic therapy may be a viable option for enhancing response rates in patients with tumorigenic stage. TSEBT may not be well tolerated in patients with erythrodermic disease, and should be used with caution. In these patients, it may be used at lower doses and with slower fractionation.[2]

## Systemic Biological Therapies

Systemic therapies are recommended for early-stage disease refractory to SDT and for advanced-stage MF and SS. The choice of systemic therapy regimens is dependent on a number of factors, including the clinical features of the patient (such as extent of patch or plaques, the burden of disease in the skin, lymph nodes and blood, previous therapies, and comorbidities), the pathological features (like presence of large cell transformation or FMF), and the immunohistochemical data (e.g., CD30 positivity).[2] Generally, systemic therapy regimens that are better tolerated for longer durations, exhibit lower rates of cumulative toxicity, and/or demonstrate higher efficacy are preferred in earlier lines of treatment. For patients requiring chemotherapy, single agents are favored over combination chemotherapy due to the higher toxicity profiles associated with multi-agent regimens and the short-lived responses observed with time-limited combination therapies. Multi-agent chemotherapy regimens are generally reserved only for disease refractory to multiple prior therapies, bulky lymph node, or solid organ disease, and/or as a bridge to alloSCT.[1,2]

Bexarotene, brentuximab vedotin (BV), mogamulizumab, vorinostat, romidepsin, and denileukin diftitox have been approved by the FDA for the treatment of MF and SS. The efficacy of BV and mogamulizumab compared with standard therapies has been demonstrated in phase III randomized trials (ALCANZA and MAVORIC, respectively). Bexarotene, vorinostat, romidepsin, and other systemic therapies, such as pralatrexate, alemtuzumab, and pembrolizumab, have only been assessed in phase II studies. Although IFNs and MTX provide clinical benefits, they have not been evaluated in phase II studies within the context of modern staging for MF and SS.[2]

## Retinoids

Bexarotene, a substrate of RXR (thus termed a "rexinoid"), is the only retinoid specifically developed for the treatment of CTCL. In 1999, the FDA and EMA approved bexarotene for use in patients with advanced-stage (IIB-IVB) CTCL who failed to respond to at least one prior systemic therapy. A Japanese study assessed the safety and efficacy of bexarotene in 139 patients with MF and reported an objective response rate of 46.8%. Patients starting treatment at 300 mg/m$^2$ showed significantly higher response rates (61.6%) compared to those on lower doses (22.6%). Additionally, among the 92 patients treated with bexarotene combined with photo(chemo)therapy, the response rate was 57.6%, which was significantly higher than the 25.5% seen in those treated with bexarotene alone. The findings of this study indicate that higher doses of bexarotene and combination therapy may enhance the treatment efficacy for MF. Common treatment-related AE were hypothyroidism (85.8%), hypertriglyceridemia (68.5%), hypercholesterolemia (43.8%), and neutropenia (21.3%). Among these, hypertriglyceridemia, hypercholesterolemia, and neutropenia were reported more frequently in patients starting treatment with bexarotene at a dose of 300 mg/m$^2$ compared to those starting at doses below 300 mg/m$^2$.[34] Laboratory monitoring of triglycerides and free thyroxine (T4) levels is essential and often necessitates additional management. Due to its favorable tolerability profile and lack of significant cumulative toxicity, the NCCN guidelines recommend bexarotene for patients with early-stage MF who do not achieve adequate disease control with SDT. It is also utilized in combination with phototherapy or ECP for early-stage disease that does not respond sufficiently to single-agent therapy, as well as for patients with advanced-stage disease.[2]

RAR agonists, such as acitretin and isotretinoin, are effective in treating early-stage MF. In a small cohort of 35 patients with early-stage MF, acitretin and isotretinoin yielded ORR of 64% and 80%, respectively, although the CR rates were low at 4% and 8%, respectively. Side effect profiles were as

previously reported for retinoids (most notably teratogenicity, dryness of skin and mucous membranes, hyperlipidemia).[35] Only moderate response rates can be achieved with retinoid monotherapy in patients with MF/SS. Therefore, these agents are often used in combination with other treatments or for maintenance therapy.[1]

## Interferon-Alpha

IFN-α exerts an immunomodulatory effect by activating $CD8^+$ T lymphocytes and natural killer cells and suppressing Th2 cytokine production in malignant T lymphocytes. IFN enhances cytotoxic effects by increasing MHC class I molecule expression in lymphocytes and inhibiting excessive production of IL-5, thereby reducing eosinophil proliferation. IFN gained prominence as a treatment modality for CTCL in 1984 and has since been incorporated into CTCL treatment guidelines worldwide.[36]

Numerous relatively small, non-randomized studies of IFN-α have been conducted in pretreated patients with MF/SS across all stages, utilizing variable dosing schedules (3-9 megaunits, three to seven times weekly). ORR > 50% and CR > 20% have been reported. Response rates are higher in the early stages and with increased IFN doses.[37]

A prospective, randomized study evaluated the efficacy of IFN combined with PUVA versus IFN combined with retinoids in patients with stage I or II CTCL. The combination of IFN and PUVA resulted in significantly higher CR rates in this patient population (70% vs. 38%).[38]

Both previously available formulations of recombinant IFN (IFN-α 2a and IFN-α 2b) have been withdrawn from the market since 2019. Given the essential role of IFN-α in the treatment of MF and SS, it is imperative that the withdrawn preparations be replaced with the sole remaining available pharmacological variant, namely pegylated IFN-α 2a (peg-IFN-α 2a).[1]

The safety, tolerability, and efficacy of peg-IFN-α 2a were prospectively evaluated by Schiller et al.[39] in an open-label, multicenter, dose-escalation study involving patients with MF stages IB-III. Patients received subcutaneous peg-IFN-α 2a at doses of 180 µg (n = 4), 270 µg (n = 6), or 360 µg (n = 3) once weekly for 12 weeks. The treatment was generally well tolerated, and the most common AE being fatigue, acute flu-like symptoms, and hepatotoxicity. Dose reductions or withholding due to AE were infrequent (n = 1 for 180 µg, n = 4 for 270 µg, and n = 0 for 360 µg). Response rates (complete or partial response) ranged from 50% to 66%, with no clear dose–response relationship observed.[39]

## Targeted Immunotherapy

### Brentuximab Vedotin

BV is an antibody-drug conjugate consisting of an anti-CD30 immunoglobulin G1 (IgG1) antibody linked to monomethyl auristatin E, a microtubule-disrupting agent, which is released upon internalization into CD30-expressing tumor cells. The standard therapeutic regimen is an intravenous infusion of 1.8 mg/kg every 3 weeks for 16 cycles or until unacceptable toxicity or disease progression occurs.[40]

Based on the results of the international, open-label, randomized phase 3 ALCANZA trial, BV has been approved for the treatment of adult patients with $CD30^+$ CTCL following at least one prior systemic therapy in Europe and the US. In this trial, BV was more effective than MTX or bexarotene in patients with ≥ stage IB MF.[41] The final analysis confirmed that BV significantly improved the ORR lasting at least 4 months (ORR4: 55% vs. 13%), as well as the median PFS (17 months vs. 4 months), and reduced patient-reported symptom burden compared with MTX or bexarotene in patients with CD30-positive MF. Peripheral neuropathy was the most common AE, reported in 44 patients (69%).[42]

In the ALCANZA trial, CD30 positivity was defined as CD30 expression in ≥ 10% of total lymphoid cells in at least one skin biopsy. The results of an exploratory analysis showed that BV resulted in higher ORR4 and improved PFS in patients with ≥ 10% CD30 expression, regardless of the large cell transformation status.[43] When addressing the practical challenge of selecting suitable patients for BV treatment, it is important to recognize that the cut-off value used in the ALCANZA trial (10% positivity) was established arbitrarily. The evidence suggests that significant responses can be observed at low positivity levels. Furthermore, CD30 expression can vary among individuals. A retrospective analysis of 135 biopsy specimens from 95 patients with MF was performed to evaluate CD30 expression by immunohistochemistry. The authors found that CD30 was detectable in 90% of the samples, with ≥ 10% positivity observed in 60%. In patients with multiple biopsies, considerable variability in CD30 expression was noted, particularly in samples obtained at different time points. The authors concluded that examining multiple tissue samples enhances the evaluation of CD30 expression in MF, potentially reducing the risk of inappropriate treatment assignment.[44]

### Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody that targets CCR4, a chemokine receptor expressed on T-cells that is involved in the cell trafficking of lymphocytes to the skin.[45]

The drug received FDA and EMA approval in 2018 for relapsed/refractory MF and SS.

The safety and efficacy of mogamulizumab were demonstrated in a large open-label, randomized, controlled phase 3 (MAVORIC) trial involving 372 patients (204 with MF and 168 with SS). Patients were randomly assigned to receive either mogamulizumab (n = 186) or vorinostat (n = 186). The trial showed a PFS of 7.7 months for mogamulizumab and 3.1 months for vorinostat, with ORRs of 28% and 4.8%, respectively. The most common drug-related AEs were infusion-related reactions, drug rash, diarrhea, and fatigue.[46] Post-hoc analyses assessing the efficacy of mogamulizumab based on blood tumor burden showed that blood involvement was correlated with improved ORRs, PFS, and time to next treatment (TTNT) among patients receiving mogamulizumab. The ORRs were 26% and 37% for patients with B1 and B2 blood involvement, respectively, and 16% for those with B0 blood involvement. The median PFS was 11 months for B2 and 8 months for B1, whereas it was only 5 months for patients with B0 involvement. The TTNT was 20 months for patients with B2 involvement, 12 months for B1, and 7 months for B0. Additionally, mogamulizumab was linked to rapid and sustained reductions in $CD4^+$ $CD26^-$ cell counts and CD4/CD8 ratios across all blood involvement categories.[47,48]

The most common AE leading to the discontinuation of mogamulizumab was drug-induced skin eruptions, which can mimic MF/SS. However, mogamulizumab-associated skin rash may serve as a potential marker of tumor response.[49] It is recommended that skin biopsies, including appropriate immunohistochemical staining and clonality assessments, be performed to rule out disease progression in patients experiencing these skin eruptions.[50]

## Alemtuzumab

Alemtuzumab is a humanized recombinant IgG1 monoclonal antibody targeting CD52.

This treatment demonstrates significant clinical activity in patients with previously treated advanced MF and SS, showing a higher ORR in patients with erythroderma or SS compared to those with advanced MF. However, it is associated with myelotoxicity and infectious complications. The subcutaneous administration of reduced-dose alemtuzumab (3-15 mg) over a shorter duration was equally effective with fewer infectious complications in patients with SS.[51] Although alemtuzumab is no longer commercially available, it can still be administered to patients with CTCL and other hematologic malignancies.[2]

## Other Immunotherapies

Immune checkpoint inhibitors, particularly anti-programmed cell death protein 1 (PD-1) and anti-PD-L1 antibodies, have transformed the treatment landscape for metastatic melanoma and other solid cancers by inducing durable responses in a significant proportion of patients with manageable immune-mediated toxicity.[1] In a phase II trial, pembrolizumab, an immune checkpoint inhibitor, demonstrated durable responses in both MF and SS, achieving an ORR of 38% with a median duration of response not reached at a median follow-up of 58 weeks. Notably, pembrolizumab was associated with a skin flare reaction, which occurred exclusively in patients with SS and correlated with high PD-1 expression in Sézary cells; this reaction must be differentiated from disease progression.[52]

KIR3DL2, a member of the KIR family of natural killer cell Ig-like receptors, is aberrantly expressed in tumor cells of most patients with SS and other CTCLs. In addition to its use in diagnosis, follow-up, and as a prognostic biomarker, targeting KIR3DL2 with IPH4102, a therapeutic monoclonal antibody, was reported to be safe and clinically active in a first-in-human phase 1 study in CTCL. A confirmed global overall response was achieved in 16 (36.4%) of 44 patients, of which 15 responses were observed in 35 patients with SS (43%).[53] A subsequent, multi-cohort, and multi-center phase II study (TELLOMAK) will evaluate the clinical activity and safety of IPH4102 alone or in combination with chemotherapy in patients with advanced T-cell lymphoma is ongoing.[1]

## Histone Deacetylase Inhibitors

HDAC inhibitors enhance the acetylation of histones and non-histone proteins, influencing gene transcription and leading to cell cycle arrest and apoptosis.

Vorinostat was the first HDAC inhibitor approved by the FDA in 2006 for the treatment of progressive, persistent, or recurrent MF/SS. In the initial phase IIB registration study, oral vorinostat (400 mg) achieved an ORR of 30%.[54] Long-term evaluation of patients on vorinostat for > 2 years indicates its safety and tolerability in patients with heavily pretreated MF/SS, with rare cumulative toxicities. However, patients should be monitored for gastrointestinal side effects, including nausea, diarrhea, and possible dehydration.[55]

Romidepsin, another HDAC inhibitor, has shown clinical efficacy across all disease compartments in treating MF/SS. The median duration of response to romidepsin ranged from 13 to 15 months. Notably, it significantly alleviated pruritus scores regardless of the clinical objective response. The ORRs were 40% for skin involvement, 35% for erythroderma, 32% for blood involvement, and 27% for lymphadenopathy.[56] When administering romidepsin, monitoring for QTc prolongation is

essential, especially when used with antiemetics, which can also affect QTc. Romidepsin is recommended as the preferred treatment for patients with SS exhibiting a great burden of Sézary cells.[2]

None of the HDAC inhibitors have received authorization for use in Europe, and they are not included in the EORTC guidelines.

### Denileukin Diftitox

Denileukin diftitox is a recombinant human IL-2 diphtheria toxin fusion protein that targets the IL-2 receptor (CD25). It was initially approved in the US for relapsed/refractory CTCL but was withdrawn from the market in 2014 due to manufacturing issues.[2] It has not been approved by the EMA for MF/SS and is therefore not included in the EORTC guidelines.[1]

A reformulated version was assessed in a study that included 69 patients with relapsed or refractory MF/SS, predominantly with stage IB-IIA (n = 25) or stage IIB (n = 24) disease. The ORR was 36%, with a median response duration of 6.5 months. Higher ORRs were observed in stage IIB patients (46%) compared with stage IA-IIA (37%) and stage III (20%). No correlation was observed between CD25 expression and treatment efficacy. The skin disease burden decreased in 84% of evaluable patients (54 out of 64). Treatment-related AE, mainly grade 1-2, included capillary leak syndrome, infusion-related reactions, visual impairment, and hepatotoxicity, with no cumulative toxicity observed.[57,58]

Denileukin diftitox is recommended in the NCCN guideline as a preferred systemic therapy for stage IIB (generalized tumor disease) and as a useful option in certain circumstances for stage IB-IIA, limited stage IIB, and stage III disease.[2]

## Chemotherapy

### Liposomal Doxorubicin

Pegylated liposomal doxorubicin exhibits single-agent activity in patients with pretreated, advanced, or refractory MF and SS. In a phase II EORTC multicenter trial involving 49 patients with relapsed/refractory advanced MF after at least two prior systemic therapies, the drug achieved an ORR of 41% (with 6% CR) and a median duration of response and median time to progression of 6 and 7 months, respectively. It was well tolerated, with no grade 3 or 4 hematologic toxicities; the most common grade 3 or 4 adverse effects were dermatologic toxicity (6%), constitutional symptoms (4%), gastrointestinal issues (4%), and infections (4%).[59]

Another real-life cohort study of 36 patients (34 with MF and 2 with SS) further confirmed the efficacy of doxorubicin, particularly in patients with tumor stage disease.[60]

### Gemcitabine

Gemcitabine, another cytostatic drug, is an effective treatment option for patients with heavily pretreated advanced-stage MF and SS. In a retrospective observational study involving 25 patients with advanced MF and SS, long-term follow-up over 15 years revealed estimated OS, PFS, and disease-free survival rates of 47%, 9%, and 40%, respectively.[61]

A single-center study of 14 heavily pretreated patients (12 with MF and 2 with SS) showed an ORR of 57%, with a median TTNT of 12 months.[62] Moreover, retrospective studies have shown favorable clinical outcomes with low-dose gemcitabine (1000 mg every 15 days), accompanied by tolerable and manageable adverse effects.[63]

### Other Chemotherapeutic Agents

The other chemotherapeutic agents included in the EORTC recommendations are chlorambucil and MTX. The recommended MTX doses range from 5 to 25 mg once weekly. Chlorambucil is used in SS in combination with low-dose prednisone. Prolonged exposure is associated with a risk of leukemia, and thus, exposure should be avoided. Due to the high efficacy of mogamulizumab in the treatment of SS, the use of chlorambucil is limited to individual patients and resource-poor settings.[1]

The NCCN guidelines recommend the use of pralatrexate in patients with heavily pretreated MF and SS. In a multicenter dose-finding study involving 54 patients with relapsed or refractory MF and SS, pralatrexate was administered at doses ranging from 10 to 30 mg/m$^2$ weekly for 2 of 3 weeks or 3 of 4 weeks, resulting in an ORR of 41% (with 6% CR). Among the 29 patients receiving the recommended dose of 15 mg/m$^2$ weekly for 3 weeks in a 4-week cycle, the ORR was 45% (with 3% CR). The most common grade 3 AE was mucositis (17%); the only grade 4 AE was leukopenia (3%).[64]

In the subgroup of patients with transformed MF treated in the PROPEL trial, pralatrexate at 30 mg/m$^2$ yielded an objective response of 25% per independent central review and 58% per investigator assessment, with median PFS and OS rates of 5 and 13 months, respectively.[65]

### Extracorporeal Photopheresis

ECP is an immunomodulating procedure that has been used for treating CTCL since 1987. The procedure is administered

over two consecutive days and is typically repeated every four weeks although it can be performed more frequently in patients with a high blood tumor burden. Responses to ECP may take up to six months to manifest, and therapy should continue until there is a loss of response.[3]

ECP can be safely applied alone or in combination with other systemic (e.g., IFN-α, retinoids) and skin-directed therapies.[66]

In a meta-analysis of over 400 patients with MF and SS, ECP as a monotherapy achieved a combined ORR of 55.7% across all stages of CTCL, with a 17.6% CR rate.[67]

A retrospective study involving 50 patients with MF reported an ORR of 42% (21 out of 50), with a median time to response of 11 months (ranging from 3 to 48 months). The OS was 72 months, showing no statistically significant differences between early-stage (77 months) and late-stage disease (69 months; $P = 0.077$). The authors concluded that the low incidence of side effects and the improved OS observed with combination therapy make ECP a viable treatment option for MF.[68] There may be an emerging role for ECP in early-stage MF; however, the available data are limited, and current guidelines do not provide recommendations in this regard.[1,69]

The degree of blood involvement, CD4/CD8 ratio, and circulating $CD3^+CD8^+$ cells or $CD4^+CD7^-$ lymphocytes have been identified as predictors of clinical response to ECP.[70,71] ECP is particularly well-suited as a systemic therapy for patients at risk of blood involvement (B1 or B2), including those with erythrodermic stage III MF or stage IVA with SS. However, there is currently no strong evidence to suggest that one combination therapy is superior to another or that ECP alone.[1]

## Hematopoietic Stem Cell Transplantation

Autologous stem cell transplantation has been abandoned in patients with MF/SS because of the invariable occurrence of relapse in all patients, despite associated toxicity. On the other hand, alloSCT is the only curative option for MF/SS in patients with advanced disease. Allogeneic transplantation is successful in part because of the graft-versus-lymphoma effect of the donor graft, but this benefit must be carefully balanced against the potential risks associated with chronic graft-versus-host disease (GVHD). A significant concern following allogeneic transplantation is the potential for disease relapse. Although some patients can be successfully treated with donor lymphocyte infusion, this can also result in severe GVHD.[3]

In a single-center retrospective study of 19 patients with advanced MF/SS who underwent autologous hematopoietic stem cell transplantation (AHSCT) (the majority of whom had progressive disease prior to the transplant), non-relapse mortality was observed to be 35.9% at 1 year and 26.9% at 3 years and beyond. The probability of OS was 48.5% and 32.3% at 1 and 5 years after transplantation, respectively. The authors noted that considering the poor prognosis for patients not receiving transplants and the absence of curative non-transplant therapies, AHSCT successfully rescued 32.3% of the transplant-eligible, heavily treated patient population within 5 years.[72]

In a systematic review and meta-analysis focusing on alloSCT in CTCL, five studies involving 266 patients were analyzed. Reduced intensity and non-myeloablative regimens were most commonly used, accounting for 76% of cases, whereas mobilized peripheral blood stem cells were the preferred graft source in 78% of patients. The pooled OS rate was 59%, and the PFS rate was 36%. The pooled relapse rate was 47%, with a non-relapse mortality rate of 19%. The findings indicate that allo-SCT provides promising OS and PFS rates; however, relapse remains a significant challenge and common cause of treatment failure. Future strategies should focus on administering allo-SCT before the onset of resistant disease and incorporating post-transplant maintenance therapies to mitigate relapse rates.[73]

In a prospective, controlled trial on alloSCT in patients with advanced MF/SS, 99 patients were enrolled, with 55 receiving alloSCT and 44 undergoing non-allogeneic therapy (patients without a compatible donor). The primary endpoint was PFS, which was significantly better in the alloSCT group (median PFS of 9.0 months after alloSCT versus 3.0 months in the matched control group). At the time of publication, the median OS was 26.9 months in the control group and was not reached in the alloSCT group. Serious AE were more common in the alloSCT group, with infections being the most common. The study concluded that alloSCT significantly improves PFS in patients with high-risk advanced-stage MF or SS who achieve remission before transplantation.[74] The decision to proceed with transplantation requires thorough counseling to weigh the significant risks against the potential long-term benefits and the options for alternative treatments.[2]

## Maintenance

Maintenance therapy refers to the ongoing administration of either skin-directed or systemic treatment after remission, with the goal of sustaining the response and preventing relapse or progression. Treatments that are deemed appropriate for maintenance should be effective, palliative, available, and simple to administer. Furthermore, they must have an excellent safety profile and exert minimal impact on the patient's quality of life.[75]

The EORTC guidelines list several agents that can be used for maintenance therapy after MF and SS. These include topical corticosteroids, chlormethine, nbUVB, PUVA, ECP, IFN-α, low-dose MTX, and oral retinoids.[1]

Currently, there is a paucity of evidence-based guidelines for the maintenance therapy of CTCL. The question of how initial remission or stable disease can be maintained is one of the most significant challenges in the management of CTCL.[76]

In practice, maintenance therapy often involves tapering the treatment that induces remission (such as phototherapy, retinoids, IFN-α, or ECP) or introducing a maintenance agent after achieving remission using a method that has dose-limiting toxicity, such as TSEB or systemic chemotherapy.[77] Overall, no definitive evidence has been available to guide the indications and selection of maintenance therapy for MF/SS. The EORTC guidelines recommend maintenance therapy for patients with a clinical stage of ≥ IB (T2b) who are at high risk of relapse and/or progression, following careful consideration and counseling.[1] In contrast, the NCCN guidelines suggest that all patients (stage IA-IV) who experience clinical benefits or have shown a response to primary treatment should be considered for maintenance therapy or tapering of their treatment regimens to enhance the duration of their response.[2]

## Supportive Care

### Management of Pruritus

Pruritus affects a large proportion of patients (nearly 90%) with CTCL and is significantly more severe in late- than in early-stage disease and in SS than in MF.[78]

The treatment of pruritus requires optimization of both SDT and systemic therapies. Daily use of moisturizers and emollients is beneficial for maintaining and protecting skin barrier. In early-stage disease, topical steroids can effectively manage both the disease and associated pruritus.[79] First-line treatment options include H1 antihistamines and gabapentin.[80] In the second-line setting, aprepitant, mirtazapine, or selective serotonin reuptake inhibitors may be considered.[81,82] If pruritus does not resolve with these agents, treatment with naltrexone may be an option.[2,83]

### Prevention and Treatment of Infections

Bacteremia/sepsis and bacterial pneumonia were identified as the primary causes of death due to infections in a retrospective cohort study of patients with MF and SS.[84] Several preventive measures can be implemented to minimize infectious complications, including maintaining and protecting the skin barrier, using bleach baths or soaks, avoiding central lines, and employing prophylactic mupirocin in cases of Staphylococcus aureus colonization. Additionally, HSV prophylaxis with acyclovir or an equivalent should be considered for patients with frequent recurrences of HSV infection.[2]

## Clinicopathological Variants of Mycosis fungoides

Clinicopathologic presentations of MF extend beyond the conventional form and include various subtypes, such as folliculotropic, erythrodermic, granulomatous, poikilodermic, hypopigmented, hyperpigmented, pagetoid reticulosis, pigmented purpura-like, bullous/vesicular, palmoplantar, hyperkeratotic/verrucous, vegetating/papillomatous, ichthyosiform, and invisible forms.[85] According to the latest World Health Organization classification of cutaneous lymphomas, only three MF variants are recognized as distinct entities with unique presentations, clinical behaviors, and treatment responses compared with classical MF. These recognized variants are FMF, pagetoid reticulosis (localized Woringer-Kolopp type), and granulomatous slack skin syndrome (GSSS).[86]

Currently, there are no guidelines specifically designed for the treatment of clinicopathological MF variants. However, information from the literature is summarized below in order to provide guidance for clinicians.

### Folliculotropic Mycosis Fungoides

FMF is the most common non-classical variant in adults. In the absence of specific guidelines, a considerable number of treatments are employed in clinical practice, with variable results. Phototherapy, in all its forms, particularly PUVA, shows the greatest initial therapeutic efficacy. In a study analyzing the treatment outcomes of 203 patients with FMF, topical steroids and UVB or PUVA phototherapy for early-stage FMF showed high efficacy, achieving an ORR of 83% (28% CR) for topical steroids and 83% and 88% for UVB and PUVA, respectively. Local RT, TSEBT, and PUVA combined with RT were more effective in patients with advanced-stage FMF, resulting in ORRs of 100% (63% CR), 100% (59% CR), and 75% (5% CR), respectively.[87] Despite their widespread use, retinoids, particularly acitretin, appear to be relatively ineffective when used together. Combination treatment with phototherapy may be advisable.[88] Patients with generalized FMF should initially be considered for single-agent systemic therapy before switching to multi-agent chemotherapy.[2]

### Pagetoid Reticulosis

Pagetoid reticulosis is characterized by an indolent clinical behavior. However, recurrence and relapse are common,

occurring at the original site or at a separate site. The minimal propensity for dissemination or extracutaneous involvement. The treatment options include TCS, topical nitrogen mustard, PUVA, nbUVB, RT, and surgery.[85]

## Granulomatous Slack Skin Syndrome

There is no specific therapeutic regimen, and the selection of a particular therapy depends entirely on the stage. Treatment options include topical nitrogen mustard, PUVA, retinoids, RT, systemic steroids, IFN-α, chemotherapy, and some combination therapies. The surgical excision of redundant skin for esthetic and functional improvement has a high relapse rate. GSSS has a slowly progressive course, with rare cases developing nodal involvement. Although the 5-year disease-specific survival of GSSS is close to 100%, its association with lymphoproliferative disorders necessitates lifelong close monitoring.[89]

## Hypopigmented Mycosis Fungoides

It is typically more prevalent in younger individuals with darker skin and a better prognosis than other types of MF. The lesions tend to persist for a long time, but respond well to TCS, TCI, nitrogen mustard, or phototherapy. In patients who present with widespread lesions at diagnosis or show rapid recent progression, the addition of IFN to the initial treatment regimen may be considered.[90]

## Bullous Mycosis Fungoides

Bullous/vesicular MF primarily affects elderly individuals and is characterized by the appearance of flaccid or tense bullae, which can develop on normal skin or within typical MF lesions. The presence of bullous lesions in MF is associated with an aggressive course and poor prognosis, as mortality within 1 year of bullous lesion development approaches 50% in reported cases.[91,92]

## Granulomatous Mycosis Fungoides

The impact of granulomatous inflammation on the prognosis of cutaneous lymphoma remains a topic of debate, as both favorable and unfavorable outcomes have been documented. In a multicenter study involving 15 patients with granulomatous mycosis fungoides (GMF), the most commonly used treatment modalities were PUVA and/or IFN-α in addition to RT. Other treatment options included TCS, imiquimod, systemic retinoids, single-agent chemotherapy, and CHOP. A disease-specific 5-year survival rate of 66% was previously identified for GMF.[93]

A systematic review of 116 cases of GMF revealed that 30% of patients developed organ metastasis, indicating that GMF is an aggressive form of MF.[94]

## Treatment in Special Patient Populations

There are currently no specific guidelines for the treatment of MF in special patient populations. However, a table has been prepared that summarizes the treatment considerations for pregnant women, pediatric and geriatric patients, and patients with renal or hepatic failure (Table 2).

## Pediatric Cases

In contrast to adults, most children with MF present with non-classic variants of the disease, which include hypopigmented, hyperpigmented, and folliculotropic forms.

In a review of 248 patients with pediatric MF, phototherapy represents the most common treatment modality. Despite the increased overall response and durability of treatment for patients receiving PUVA compared with UVB therapy, nbUVB is commonly regarded as the primary treatment modality for pediatric MF because of its more favorable side effect profile.[95] The British Phototherapy Group does not recommend the use of oral psoralen in children aged 10 years given the difficulty in ensuring adequate eye protection.[96]

TCS was frequently combined with phototherapy. Other topical agents, such as retinoids, nitrogen mustard, imiquimod, and TCI, were occasionally used in pediatric patients. Oral retinoids and MTX, as well as combinations of systemic therapies with SDTs, have been applied as advanced treatment in a small number of patients and have shown variable efficacy. In selecting an appropriate therapy for pediatric patients, it is of paramount importance to consider the risk-benefit ratio.[97]

## Pregnancy

The impact of pregnancy on MF is controversial, with some reports suggesting that pregnancy negatively influences disease progression,[87] while others indicate no effect on early MF.[98] Treatment options for pregnant patients diagnosed with malignancy present unique ethical challenges because of the competing responsibilities toward both the mother and fetus. The ethical dilemma becomes more pronounced in advanced CTCL cases.

While uncomplicated pregnancies and healthy births can occur during treatment for early-stage disease, the systemic therapies recommended for advanced MF carry heightened risks for the fetus. The effects of radiation on the fetus depend on gestational age and include an increased risk of congenital

**Table 2. Treatment in special patient populations***

| | Pregnancy category | Pediatric use | Geriatric use | Kidney failure | Liver failure |
|---|---|---|---|---|---|
| Potent TCS (clobetasol cream) | Not assigned (use on the smallest area of skin, for the shortest duration possible) | NR (due to potential HPA axis suppression) | Start with the low end of the dosing range | NS | NS |
| Topical mechlorethamine | Category D (can cause fetal harm) | ND | Cutaneous adverse reactions and discontinuation of treatment more common | NS | NS |
| Topical retiroids | Category X (contraindicated) | Tazarotene-safety and efficacy have been established in patients ≥ 9 years old<br>Bexarotene-ND | NS | NS | NS |
| Topical imiquimod | Category C (used only if the potential benefit justifies the potential risk to the fetus) | NR for patients < 12 years of age | NS | NS | NS |
| TCI | Category C | Not indicated for < 2 years of age | NS | NS | NS |
| Methoxsalen (for PUVA) | Category D | ND but should not be used in children < 12 years of age | NS | NS but should not be used in patients with severe renal impairment | NS but should not be used in patients with severe hepatic impairment |
| Oral retiroids | Category X | ND | Start with the low end of the dosing range | Contraindicated in patients with severely impaired kidney function | Contraindicated in patients with severely impaired liver function |
| Pegylated IFN-α | Category C | Safety and efficacy in patients < 5 years old have not been established | Neuropsychiatric, cardiac, and systemic (flu-like) adverse reactions may be more severe | Dose should be reduced in patients with CLcr < 30 mL/min | Hepatic function should be closely monitored |
| Brentuximab vedotin | Category D | ND | NS | Avoid the use in patients with severe renal impairment (CLcr < 30 mL/min) | Avoid the use in patients with moderate or severe hepatic impairment |
| Mogamulizumab | Not assigned | ND | Similar effectiveness but higher risk of side effects | NS | NS |
| Pembrolizumab | Category D | ND | NS | NS | No dose adjustment is needed for mild hepatic impairment,<br>ND for moderate or severe impairment |
| Histone deacetylase inhibitors | Category D | ND | NS | Patients with end-stage renal disease should be treated with caution | Use with caution in moderate to severe hepatic impairment |
| Denileukin diftitox | Not assigned<br>No human or animal data<br>Use only if clearly needed | ND | ND | NS | NS |
| Doxorubicin | Category D | ND | NS | ND | Dosage should be reduced in patients with impaired hepatic function |
| Gemcitabine | Not assigned but can cause fetal harm when administered to a pregnant woman | ND | NS | ND | ND |
| Methorexate | Category X for non-neoplastic diseases like psoriasis and rheumatoid arthritis<br>Not assigned for all other conditions | Safety and efficacy have been established for treatment of ALL and pJIA but not for other indications | ND | Closely monitor patients with renal impairment (CLcr < 90 mL/min)<br>Reduce the dosage or discontinue as appropriate | Closely monitor patients with hepatic impairment for adverse reactions<br>Reduce the dosage or discontinue as appropriate |

TCS: Topical cortocosteroids, NR: Not recommended, HPA: Hypothalamic-pituitary-adrenal, NS: Not specified, ND: No data (safety and effectiveness have not been established), TCI: Topical calcineurin inhibitors, PUVA: Psoralen plus ultraviolet-A, IFN-α: Interferon alpha, ALL: Acute lymphoblastic leukemia, CLcr: Creatinine clearance, pJIA: Polyarticular juvenile idiopathic arthritis, *The data presented in the table were sourced from the FDA website (accessdata.fda.gov)

malformations and future childhood cancer. Chemotherapy may increase the risk of teratogenesis, spontaneous abortion, congenital malformation, and fetal death.

Teratogenesis has been demonstrated in animal models using conventional systemic cytotoxic agents (alkylating agents, antimetabolites, and mitotic inhibitors).[99]

The data on fetal risk are based on the standard FDA pregnancy categories (A, B, C, D and X) and are presented in Table 2.

### Organ Transplant Recipients

A rare complication of transplantation is the development of post-transplant lymphoproliferative diseases (PTLD). Most cases originate from B-cells, whereas those arising from the T-cell lineage are less common. The incidence of PTLD varies depending on the organ type, with multiorgan/intestinal transplantation being the most common.[100] Managing PTLD is challenging because it requires carefully balanced therapies that minimize the risk of graft rejection while avoiding excessive lymphoproliferation. The initial treatment approach often involves the reduction, modification, or discontinuation of immunosuppressive drugs. In addition, classical MF is frequently treated with SDTs, such as topical corticosteroids or PUVA. Systemic retinoids are also preferred due to the absence of immunosuppressive effects.[101] The safety and efficacy of pegylated IFN treatment in patients undergoing organ transplantation have not been established. As with other alpha INFs, liver and renal graft rejections have been reported for pegylated IFN.[102]

### Limitations and Future Research Needs

Many of the recommendations for the treatment of MF/SS are based on relatively low-quality evidence. The majority of studies included fewer than 50 participants, none evaluated expectant management as a control, and few assessed quality of life. In addition, when assessing treatment efficacy, it remains difficult to identify and record measures of therapeutic success that accurately reflect the benefit to the patient. The paucity of participants in existing studies on this rare disease presents a significant challenge in conducting research on a diverse and individualized range of treatment options. For effective research to be conducted in the future, it is essential that standardized measures of disease response, clearly defined meaningful endpoints and uniformly reported prognostic markers are in place.[103]

## Conclusion

The most recent evidence-based recommendations for the treatment of MF and SS have been extracted from international guidelines. Generally, patients with early-stage disease should undergo SDT as their initial treatment. In the event of relapse, patients should receive additional courses of the same SDT or consider alternative treatment options. Systemic therapy should primarily be considered for patients with advanced-stage refractory cutaneous disease. Currently, there is no established treatment for refractory disease that can consistently produce reliable, durable remissions, or curative results. All patients with refractory disease should participate in multicenter clinical trials. Furthermore, maintaining quality of life should be a primary objective of therapeutic strategies and should be evaluated in clinical trials along with response rates.

### Footnotes

### Authorship Contributions

Concept: H.Ş., H.M.E.M., Design: H.Ş., H.M.E.M., Data Collection or Processing: H.Ş., H.M.E.M., Analysis or Interpretation: H.Ş., H.M.E.M., Literature Search: H.Ş., H.M.E.M., Writing: H.Ş., H.M.E.M.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Review

# Follow-up of Mycosis Fungoides

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## Abstract

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphoma with an indolent course. The tumor, node, distant metastasis, and blood (TNMB) staging system is still the best method for determining prognosis. Individualized, TNMB-compliant conservative treatment approach is the basis of MF patient management. Treatment responses should be evaluated according to standardized guidelines based on objective criteria. There is no consensus on the follow-up of patients with cutaneous lymphoma, and the frequency of follow-up should be planned individually for life, depending mainly on disease stage; primary cutaneous lymphoma subtype; and the treatment agent used.

**Keywords:** Mycosis fungoides, follow-up, TNMB staging, precision medicine

## Introduction

Primary cutaneous lymphomas are non-Hodgkin lymphomas of T- and B-cells that typically present in the skin without any extracutaneous disease findings upon diagnosis. Cutaneous T-cell lymphomas (CTCL) constitute approximately 75-80% of primary cutaneous lymphomas. Mycosis fungoides (MF) accounts for 54-72% of primary CTCL (Figure 1). The primary cutaneous lymphoma classification revised by the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) in 2018 is still accepted (Table 1).[1-3] Given that CTCLs have a different clinical presentation and prognosis compared to nodal lymphomas that secondarily involve the skin, patient management requires distinct approaches. A personalized, TNMB-compliant (Table 2) conservative treatment strategy is the cornerstone of managing patients with MF. The treatment of each case diagnosed with MF based on clinical, histopathological, and immunohistochemical findings should be individually planned in accordance with the current literature. According to the TNMB staging system, early-stage cases (IA-IIA) can be managed with skin-directed therapies, whereas advanced-stage cases (IIB-IVB) should be treated with systemic therapies, either as monotherapy or in combination with skin-directed therapies, utilizing a multidisciplinary approach.[4-6]

In this section, the key aspects of MF patient management are discussed in accordance with the current literature.

### Which Examination is Right for Which Patient?

The primary objectives of the tests conducted during the diagnosis and follow-up of patients are to determine the stage of the disease, identify whether the clinical course is aggressive or indolent, assess the suitability of metabolic parameters for the planned treatment, detect any comorbidities that may accompany the condition, evaluate the treatment response (complete/partial response, stable disease, progression, and relapse), and monitor treatment-related side effects.[4-6]

**Submission:** 23-Sep-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 07-Oct-2024

Access this article online

Quick Response Code:

Website: www.turkjdermatol.com

DOI: 10.4274/tjd.galenos.2024.60352

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**How to cite this article:** Yazici S, Aksakal E. Follow-up of mycosis fungoides. Turk J Dermatol. 2025;19(1):61-67.

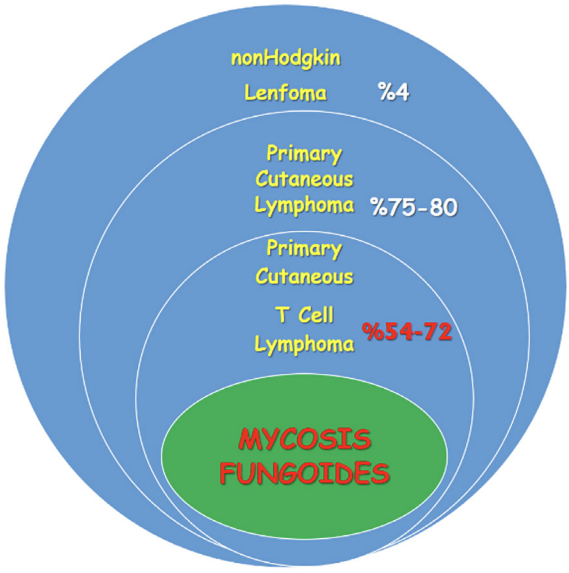


**Figure 1.** Frequency of primary cutaneous lymphomas

**Detailed physical examination:** From the first presentation of the patient, a detailed physical examination including scalp and mucosa examination is required at each visit for initial staging and follow-up visits, lesion type; extent; suspicious (≥ 1.5 cm) palpable lymph node (LN) and organomegaly evaluation.[4-6]

**Histopathological and İmmunohistochemical examination:** Histopathological and immunohistochemical diagnostic criteria for MF were first defined in 2005 for clinically suspicious skin lesions and are still widely accepted today.[7] For histopathological examination during the initial presentation and follow-up, at least two skin biopsies should be taken from different anatomical regions and lesions with varying morphologies (indurated and scaly), using a punch biopsy instrument of at least 4 mm. In cases with high clinical suspicion in which a diagnosis cannot be confirmed histopathologically and immunohistochemically at the initial staging, close follow-up with repeat biopsies is crucial. Clinicopathological correlation is essential for an accurate diagnosis.[4,5]

**Table 1. Cutaneous T-cell lymphoma WHO-EORTC classification, frequency and prognosis**

| Revised WHO 2018 classification | Frequency, (%) | 5-y DSS, (%) |
|---|---|---|
| **Cutaneous T- and NK-cell lymphomas** | | |
| MF | 39 | 88 |
| **MF variants;** | | |
| Folliculotropic MF | 5 | 75 |
| Pagetoid reticulosis | < 1 | 100 |
| Granulomatous slack skin | < 1 | 100 |
| Sézary syndrome | 2 | 36 |
| Adult T-cell leukemia/lymphoma | < 1 | NDA* |
| **Primary cutaneous CD30⁺ LPDs;** | | |
| C-ALCL | 8 | 95 |
| LyP | 12 | 99 |
| Subcutaneous panniculitis-like T-cell lymphoma | 1 | 87 |
| Extranodal NK/T-cell lymphoma, nasal type | < 1 | 16 |
| Chronic active EBV infection | < 1 | NDA* |
| **Primary cutaneous peripheral T-cell lymphoma, rare subtypes;** | | |
| Primary cutaneous γ/δ T-cell lymphoma | < 1 | 11 |
| CD8⁺ AECTCL (provisional) | < 1 | 31 |
| Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder (provisional) | 6 | 100 |
| Primary cutaneous acral CD8⁺ T-cell lymphoma (provisional) | < 1 | 100 |
| Primary cutaneus peripheral T-cell lymphoma, NOS* | 2 | 15 |
| **Cutaneous B-cell lymphomas** | | |
| Primary cutaneous marginal zone B-cell lymphoma | 9 | 99 |
| Primary cutaneous follicle center lymphoma | 12 | 95 |
| Primary cutaneous large B-cell lymphoma (leg type) | 4 | 56 |
| EBV1 mucocutaneous ulcer (provisional) | < 1 | 100 |
| Intravascular large B-cell lymphoma | < 1 | 72 |

WHO: World Health Organization, DSS: Disease-specific survival, NK: Natural killer, MF: Mycosis fungoides, NDA*: No data available, LPDs: Lymphoproliferative disorders, C-ALCL: Cutaneous anaplastic large-cell lymphoma, LyP: Lymphomatoid papulosis, EBV: Epstein-Barr virus; **γ/δ**: Gamma/delta, AECTCL: Aggressive epidermotropic cytotoxic T-cell lymphoma, NOS*: Not otherwise specified

**Table 2. Mycosis fungoides TNMB staging**

| Clinical stage | T(skin) | N(node) | M(Visceral) | B(blood involvement) |
|---|---|---|---|---|
| IA (limited skin involvement) | T1 (patches, papules, and/or plaques covering < 10% BSA) | N0 | M0 | B0 or B1 |
| IB (skin only disease) | T2 (patches, papules, and/or plaques covering ≥ 10% BSA) | N0 | M0 | B0 or B1 |
| IIA | T1-2 | N1-2 | M0 | B0 or B1 |
| IIB (tumor stage disease) | T3 [one or more tumors (≥ 1 cm in diameter)] | N0-2 | M0 | B0 or B1 |
| IIIA (erythrodermic disease) | T4 (confluence of erythema ≥ 80% BSA) | N0-2 | M0 | B0 |
| IIIB (erythrodermic disease) | T4 (confluence of erythema ≥ 80% BSA) | N0-2 | M0 | B1 |
| IVA1 (Sézary syndrome) | T1-4 | N0-2 | M0 | B2 |
| IVA2 (Sézary syndrome or non-Sézary) | T1-4 | N3 | M0 | B0 or B1 or B2 |
| IVB (visceral disease) | T1-4 | N0-3 | M1A or M1B | B0 or B1 or B2 |

BSA: Body surface area, T: Tumor, N: Node, M: Metastasis, B: Blood

In the evaluation of treatment response, histopathological confirmation is required in cases of suspected residual disease, the presence of resistant lesions, a different clinical presentation, lack of response or progression, aggressive clinical behavior, or suspicion of relapse in patients who have achieved complete remission. If the disease remains stable, performing a biopsy is left to the clinician's discretion.[7,8]

Additionally, the prognosis of the folliculotropic MF variant, as defined in the WHO-EORTC classification, differs from that of classic MF.[1,9,10] Another significant histopathological finding is large cell transformation (LCT), which may indicate a poor prognosis. Therefore, histopathological and immunohistochemical examination is necessary to differentiate between MF with LCT and other $CD30^+$ clinicopathological conditions.[5,11]

**1.3. Laboratory examination:** In the first admission and follow-up, blood tests should include complete blood count [including lactate dehydrogenase (LDH)]; comprehensive biochemical tests; liver and kidney function tests, and viral serology [hepatitis markers, human immunodeficiency virus, human T-cell lymphotropic virus 1 (HTLV-1)] at the first admission. Given the potentially advanced age of patients with MF and immunosuppressive nature of the disease, secondary malignancies that may accompany metabolic comorbidities should be considered. Each patient should be approached holistically, and necessary tests should be conducted in accordance with national and international guidelines to rule out age- and sex-appropriate malignancies.[5,12-14]

**Peripheral blood smear and flow cytometric analysis:** Although peripheral blood smear is performed at the initial evaluation and during follow-up visits, as needed, to assess Sézary cells, it provides subjective results. The use of flow cytometry to determine the absolute counts of Sézary cells is becoming increasingly widespread. According to EORTC and European Society for Medical Oncology (ESMO) guidelines, flow cytometry is recommended for the diagnosis and follow-up of all patients suspected of having blood involvement.[6,15]

Flow cytometric analysis should be performed in cases of stage IIB and advanced stages, generalized patch or plaque involvement (stage T2A/T2B), erythroderma, persistent pruritus, lymphocytosis, elevated serum LDH levels, and treatment resistance. In patients with initial pathological flow cytometry, follow-up flow cytometric evaluation every 3 months is recommended.[16,17]

***TCR* gene clonality:** *TCR* gene clonality can be observed in both malignant and benign conditions and may not be present in all MF lesions. While demonstrating identical clones in the skin, blood, and/or LN simultaneously can be useful in the diagnosis and differential diagnosis of MF, it is not absolutely recommended in guidelines due to its limited availability.[4-6]

## Evaluation of Treatment Response

In patients with MF, decisions regarding whether to continue, discontinue, or change treatment are primarily based on clinical evaluation, although treatment responses may vary between compartments (skin, LN, blood, internal organs). The International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the EORTC have published Consensus Guidelines for Treatment Response Evaluation Criteria. Depending on the initial characteristics of the case, treatment responses may differ across compartments; therefore, the treatment responses of the skin, LN, blood, and internal organs should be evaluated separately.[18]

**Evaluation of treatment response in skin involvement:** Complete clearance of the skin lesions after treatment is considered complete response. A biopsy of clinically normal-appearing skin is not required to confirm complete response. However, if there is any suspicion of residual disease (persistent erythema/pigmentary changes), the response should be evaluated histopathologically. If histopathological examination reveals finding indicative of MF, the treatment response is considered a partial response. In patients with isolated skin involvement who are not in the tumoral stage (T3), a 50-99% improvement in lesions without the development of new tumors is considered a partial response in T1, T2, and T4 stages. A reduction of less than 50%, no change in lesions, or up to a 25% increase is considered stable disease. The development of a new tumor (T3) in patients with T1, T2, or T4 skin involvement or an increase of more than 50% in the skin score in patients who achieved a complete or partial response is considered progressive disease. The emergence of any clinical signs associated with MF during follow-up of patients who achieved complete response is considered a relapse.

**Evaluation of treatment response in lymph node involvement:** Patients with LN involvement that are the largest in the draining area near the lesion, show high positron emission tomography (PET) uptake, and have a long axis ≥ 1.5 cm, short axis ≥ 1 cm, hard, irregular, clustered, or fixed, an excisional biopsy should be performed. The excised material should be evaluated histopathologically, immunohistochemically, and if possible, for TCR clonality. In the presence of multiple LNs, the decision for excisional biopsy should prioritize Cervical > Axillary > Inguinal LNs.

Although physical examination is a valuable method in the evaluation of LNs, it is insufficient on it's own for accurately determining their size.[19] Given the variations among evaluators, the use of contrast-enhanced computed tomography (CT) (cervical, thoracic, abdominal, pelvic) provides more objective results in the evaluation of LNs compared with ultrasound.[20]

In the PROspective Cutaneous Lymphoma International Prognostic Index (CLIPi) study, which examined the long-term follow-up of early-stage patients, it was emphasized that physical examination alone is a poor predictor of LN enlargement or involvement; the presence of plaque lesions may indicate LN involvement in early-stage MF patients and is important in deciding who should undergo imaging. Additionally, imaging could increase the detection rate of stage IIA MF and identify patients with rare extensive LN involvement, potentially upgrading them to advanced stage (IVA2).[20] PET/CT has been identified as more sensitive than CT alone in detecting lymphoma-related LN involvement for MF staging, and the intensity of PET activity has been shown to correlate with the histological grade of LN involvement. It has been reported that PET/CT can provide more accurate staging and prognostic information.[21,22]

In the assessment of LN treatment response, the initial method considers a complete response when, after treatment, the largest transverse diameter (long axis) of all LNs is ≤ 1.5 cm. For LNs classified as N3 prior to treatment, where the long axis is ≤ 1.5 cm but the short axis is > 1 cm, a complete response is defined as the short axis being reduced to ≤ 1 cm after treatment or an LN biopsy result that is negative for lymphoma.

A partial response to treatment is defined as a ≥ 50% reduction in the Sum of the Product of Perpendicular Diameters (SPD), calculated by multiplying the largest transverse and vertical diameters of each pathological LN compared with baseline. Additionally, no new pathological LN should develop with a long axis greater than 1.5 cm, or if the long axis is between 1 and 1.5 cm, no new LN should have a short axis greater than 1 cm.[23] Progressive disease is defined as a ≥ 50% increase in the SPD of pathological LNs compared with baseline, the development of a new pathological LN proven to be N3 histologically with a long axis greater than 1.5 cm or a long axis between 1-1.5 cm with a short axis greater than 1 cm, or a > 50% increase in the SPD of LNs that previously met the criteria for partial response. Cases that do not meet the criteria for complete response, partial response, or progressive disease are classified as stable disease. In a patient who achieved complete response to treatment, the development of a new LN was proven to be N3 histologically, with a long axis of 1.5 cm is considered a disease relapse.

**Evaluation of treatment response in visceral disease:** In the evaluation of organ involvement, it is recommended to confirm organ involvement, except for liver and spleen involvement, which can be determined by appropriate imaging methods, through biopsy at the initial assessment.[5] The assessment of bone marrow involvement as either organ involvement or a separate prognostic factor in patients with Sézary syndrome (SS) has not been clearly established in the studies conducted. Therefore, in many studies, bone marrow involvement is considered part of blood involvement and does not need to be taken into account when evaluating the treatment response of visceral involvement.[24] In cases in which imaging is insufficient for the initial assessment of organ involvement, the diagnosis should be confirmed by biopsy.

Criteria for complete response after treatment: any organ that initially showed involvement should not appear enlarged on physical examination or imaging and should be observed as normal. Nodules should be present on liver or spleen imaging. Any mass observed on post-treatment imaging should be

biopsied to rule out a lymphoma diagnosis. An increase in liver or spleen size without new sites of involvement, along with a reduction of 50% or more in the SPD value of pre-existing liver and spleen nodules or any organ involvement after treatment, is considered a partial response. The presence of new organ involvement, more than 50% progression in the organ previously affected before treatment (to be determined by SPD value), or a loss of more than 50% of the response in a patient who had previously achieved partial response, constitute progressive disease. Conditions that do not meet the criteria for complete response, partial response, or progressive disease are classified as stable disease, whereas the observation of new organ involvement in a patient who previously achieved complete response should be considered a relapse.

In cases of localized skin recurrence in which no tumoral lesions are present, existing tumors show signs of regression, and no organ symptoms are evident; therefore, imaging is not necessary in asymptomatic early-stage patients. However, in patients with stage ≥ IIB, imaging should be used to evaluate the patient if new lymphadenopathy develops, in case of unexplained laboratory findings, histopathological examination reveals LCT or folliculotropism, or if clinical progression is detected.[4-6]

## Prognosis

Rare cases of MF usually present with early-stage disease with a median survival of 10-35 years, but more than 25% progress to advanced disease with a median survival of less than 4 years.[25]

The CLIPi, developed from another retrospective cohort study of 1,502 patients with MF and SS in the United Kingdom, identified unfavorable factors in patients with early stage (IA-IIA) as male gender; age > 60 years; presence of plaque lesions; folliculotropic disease, and N1/Nx classification, whereas unfavorable factors in advanced stage (IIB-IVB) disease were male gender; age > 60 years, B1/B2, N2/3, and visceral involvement. In a retrospective study of 1,275 patients with advanced-stage MF or SS from 29 international centers, extracutaneous disease (stage IV), age > 60 years, transformation to large cell histology and increased LDH levels were independently associated with worse overall survival.[26,27]

Although clinical, demographic, hematologic, histopathologic, and genetic abnormalities associated with poor prognosis have been identified in addition to the TNMB staging system, these studies are small, single-center cohorts with inconsistencies. Therefore, the findings should be validated through large-scale, prospective, multicenter international studies. The TNMB staging system remains the best method for determining prognosis.

## Follow-up Frequency

In patients with MF, cutaneous lymphoma, follow-up recommendations are for patients in complete remission, and treatment should be continued in patients with stable disease or partial remission. The goals of follow-up in patients with cutaneous lymphoma are to detect relapses and metastases, identify secondary lymphomas, and monitor for treatment-related side effects (such as psoralen photochemotherapy associated tumors). All patients with cutaneous lymphoma should be educated to regularly perform self-examination of their skin and palpation of LNs. Follow-up should be individualized based on clinical needs, and should be conducted throughout life.

There is no consensus regarding the follow-up of patients with MF and cutaneous lymphoma, and the follow-up intervals should be individually tailored according to the disease stage, primary cutaneous lymphoma subtype, and treatment agents used. According to the ESMO guidelines, for indolent types of cutaneous lymphoma, follow-up is recommended every 6-12 months for patients with stable disease or those in complete remission, whereas for active and progressive disease, follow-up visits are recommended every 4-6 weeks. These visits should primarily be based on patient history and physical examination, with additional tests (blood tests, histopathological examination, imaging) conducted only when necessary. Since relapses after complete remission or tumor response are often localized to the skin, there is generally no need to routinely use imaging methods in all follow-up visits after treatment.[6]

According to the S2k Guidelines, patients initially diagnosed with stage IA and IB should undergo detailed history-taking and physical examinations every 6 months for the first 5 years and annually thereafter. In this patient group, imaging methods such as LN ultrasound, CT, PET/CT, and blood tests are not necessary unless there is a suspicion of recurrence based on physical examination and history. Patients with stage IIA should undergo detailed history and physical examination every 3 months for the first 2 years, every 6 months in the 3$^{rd}$, 4$^{th}$, and 5$^{th}$ years, and annually thereafter. Regular LN ultrasonography and laboratory tests, including complete blood count and LDH levels, are recommended for follow-up. For patients with blood involvement beyond B0, Sézary cell counts and flow cytometric analysis are required during follow-up after remission. The frequency of follow-up for patients with advanced-stage disease should be determined on an individual basis.[4,15]

## Conclusion

In the National Comprehensive Cancer Network Guidelines, although there are no specific recommendations regarding the follow-up frequency for patients with MF, the 2024 version of the Peripheral T-cell Lymphoma Guidelines suggests clinical and histopathological evaluations every 3-6 months during the first 2 years, followed by as-needed evaluations based on clinical necessity. Imaging methods are recommended every 6 months for the first 2 years, once annually between years 2 and 5, and thereafter only as clinically indicated.[5]

### Footnotes

### Authorship Contributions

Concept: S.Y., E.A., Design: S.Y., E.A., Data Collection or Processing: S.Y., E.A., Analysis or Interpretation: S.Y., E.A., Literature Search: S.Y., E.A., Writing: S.Y., E.A.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

**Financial Disclosure:** The authors declared that this study received no financial support.

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Original Article

# Investigating the Role of YouTube in Disseminating Information on Mycosis Fungoides: The Most Common Skin Lymphoma and Eczema Mimicker

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## Abstract

**Aim:** Mycosis fungoides (MF) is the most prevalent cutaneous lymphoma. It is often detected late and can resemble a variety of dermatologic illnesses. Early diagnosis and understanding of the disease are essential, knowledge is accessible through the internet and various social media channels such as YouTube, a popular and easily accessible platform for sharing video information on various topics. This study aimed to analyze the information content of YouTube regarding MF.

**Materials and Methods:** Separate searches on YouTube were conducted using the keywords "MF," "cutaneous lymphoma," and "Sézary syndrome," resulting in 101 videos included in our study. We utilized the DISCERN scale, the Journal of the American Medical Association (JAMA) scale, and the Global Quality Scale (GQS) to assess the content, reliability, and quality of the video information.

**Results:** Seventy-six videos (75.2%) contained evidence-based material, while 25 (24.8%) did not. Professional health institutions/foundations were the most common video uploaders (n = 42, 41.6%), followed by medical journals (n = 10, 9.9%). All videos received a mean DISCERN Score of 42.76 (indicating moderate quality), a mean JAMA score of 2.10 (indicating moderate reliability and accuracy), and a mean GQS score of 2.51 (indicating low to medium quality).

**Conclusion:** Unlike many diseases everyone can comment on, those who upload videos about MF are professionals on this subject, so most of the videos on YouTube about MF are evidence-based and of moderate quality. Dermatologists, who play a crucial role in diagnosing and treating this condition, should share more of their knowledge on YouTube.

**Keywords:** YouTube, mycosis fungoides, video

## Introduction

The most prevalent cutaneous T-cell lymphoma is mycosis fungoides (MF). It appears clinically as inflammatory erythematous plaques or patches, with epidermotropism typical of its early-stage histology. However, various atypical MF genres have recently been identified in the literature as both clinical and histological, and they can resemble any dermatological skin condition.[1] Unfortunately, there is often a delay between the first symptom and the initial diagnosis of MF. A multicenter study (n = 430, 29 centers, 15 countries) discovered that the diagnosis was made on average 36 months later than expected.[2] As a result, diagnosing MF, understanding its various symptoms, and raising patient awareness are critical.

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**Submission:** 17-Dec-2024 **Web Publication:** 18-Mar-2025
**Acceptance:** 06-Jan-2025

Access this article online

Quick Response Code:

Website: www.turkjdermatol.com

DOI: 10.4274/tjd.galenos.2025.08370



**How to cite this article:** Menteşoğlu D, Kurmuş GI, Kartal SP. Investigating the role of YouTube in disseminating information on mycosis fungoides: the most common skin lymphoma and eczema mimicker. Turk J Dermatol. 2025;19(1):68-73.

 

The stage and severity of the disease determines MF treatment. Non-aggressive treatment options such as topical therapy and ultraviolet A irradiation are recommended in the early stages. Allogeneic stem cell transplantation may be beneficial in advanced-stage patients. Although traditional systemic and single-agent therapies are feasible, recurrences are inevitable. Various monoclonal antibodies are also used in the treatment of some patients.[3]

Social media use is increasing drastically in the modern day. YouTube is one of the most widely recognized video publishing networks. This platform is increasingly becoming the primary source of learning and teaching material.[4] YouTube is a popular social networking platform with visual and audio features that appeal to individuals of all ages. It can spread information and influence public opinion.[5] However, there is also the risk of incorrectly disseminating health-related information.[4] In addition, the anonymity of video access improves accessibility to medical information.[6]

So far, no study has investigated MF videos on YouTube. Therefore, in this cross-sectional study, we aimed to evaluate the content, reliability, and quality of MF-related information presented in YouTube videos using the Global Quality Scale (GQS),[7] the Journal of the American Medical Association (JAMA) Benchmark criteria,[8] and DISCERN scale.[9]

## Materials and Methods

On May 8, 2023, we conducted three separate YouTube searches using the terms MF, cutaneous lymphoma, and Sézary syndrome. Before entering each search term, we cleared YouTube's existing browsing data was wiped. We then scanned the 100 most viewed videos from each query result, sorted by the YouTube search filter. However, there were only 57 videos in the Sézary syndrome search, resulting in a total of 257 videos being reviewed for the study. Of these, 156 were excluded because they were not in English, were the same video, or because they were unrelated to the subject. Consequently, 101 videos were included in the final stage (Figure 1).

The duration, upload date, type of uploader, country of upload, number of views, number of subscribers of the uploader, number of likes/dislikes, and comments were all recorded for each video included in the study. Additionally, video interaction was calculated using the interaction index (IR): (Number of likes - number of dislikes)/total number of views x100%.[10]

The videos were then manually assessed by two dermatologists, who were unaware of each other's ratings. A board-certified dermatologist reviewed any inconsistencies or differences in video categorization. We also note information such as whether the videos were evidence-based, provided and promoted medical prescription therapies, critiqued consultation with healthcare providers, and encouraged the search for a medical expert. Furthermore, the video content type (MF disease definition, symptoms, diagnosis, causes, risk factors, treatments, medications used in treatment, prognostic variables, and follow-up) was documented. The quality and reliability of the health information in all videos were evaluated by two independent dermatologists using content assessment methods, the JAMA criteria, and the DISCERN scale, as well as the educational value using the GQS. According to the average DISCERN score assessment, video uploader types were split into five groups: group 1 (very poor: 16-26 points), group 2 (poor: 27-38 points), group 3 (moderate: 39-50 points), group 4 (good: 51-62 points), and group 5 (excellent: 63-75 points).

This study did not involve any human or animal participants; no ethics committee approval was required, as the study analyzed publicly available data.

### Statistical analysis

For statistical analysis, SPSS version 29.0 was employed. Descriptive analyses for both categorical and numerical variables were carried out, Pearson's chi-square test was used for categorical data, and the Kolmogorov-Smirnov test was performed to determine the normality of the distribution. The Kruskal-Wallis test was used to assess whether there was a significant difference in mean scores of views, likes, dislikes, number of comments, and IR between groups 1-5. As there was no normal distribution, the difference between

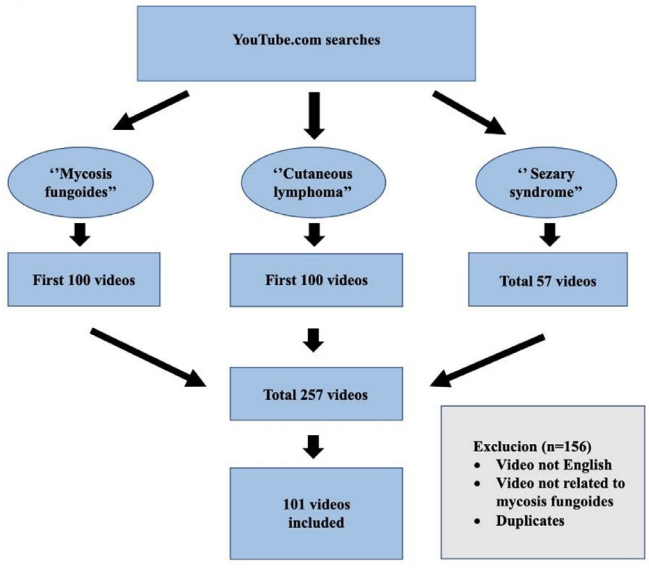


**Figure 1.** Video selection process about mycosis fungoides for YouTube searches

the average DISCERN, JAMA, and GQS scores of the video uploaders was examined using the Kruskal-Wallis test. The Cohen kappa test was used to assess inter-rater reliability, and a *P* value of 0.05 was utilized for all statistical tests to determine statistically significant differences.

## Results

In the study, 101 videos were evaluated and categorized: 23.8% were uploaded by healthcare providers, while 76.2% were uploaded by non-healthcare providers 75.2% of the videos contained evidence-based material, while 24.8% did not. The most frequent video uploader was a professional health organization/foundation (n = 42, 41.6%), followed by a medical journal (n = 10, 9.9%). Table 1 lists all the characteristics of YouTube videos about MF.

The United States of America uploaded, with professional health organizations/foundations and medical journals uploading about half of them. Each of the videos obtained a mean DISCERN score of 42.76 (moderate quality), a mean JAMA score of 2.10 (moderate reliability and accuracy), and a mean GQS score of 2.51 (low-moderate quality) (Table 1). The Cohen kappa was used to estimate interrater reliability, and it revealed an almost perfect correlation for DISCERN (0.88), JAMA (0.83), and substantial agreement for GQS (0.68).

Group 1 had the most significant views out of the five groups (Table 1). However, the groups had no statistically significant difference between the groups ($P = 0.35$). The average number of video likes and IRs in group 1 was statistically significant differences ($P = 0.016$ and $P = 0.019$, respectively). The video time in group 1 was the least (6.22), and the longest (45.79), and it was statistically significant ($P < 0.001$) (Table 2).

Among video uploaders, the professional organization/foundation (52.07) and dermatologist (52.00) categories had the highest DISCERN scores, while the patient (26.75) and non-profit personal channels (26.89), had the lowest. This distinction between groups was also statistically significant ($P < 0.001$) (Table 3). Moreover, the highest JAMA scores were given to professional health organizations/foundations (2.69) and universities (2.67). In contrast, the lowest scores were reported in non-profit personal channels (0.67) and patients (0.75), with a statistically significant difference between video uploaders ($P = 0.001$). Furthermore, dermatologists (3.33) and professional health organizations/foundations (3.24) had the highest GQS scores, while patients (1.25) and pharmaceutical companies (1.33) had the lowest. There was a statistically significant difference in scores between video uploaders ($P = 0.005$) (Table 3).

**Table 1. Features of the YouTube videos regarding mycosis fungoides**

| | |
|---|---|
| **Video loading time** | |
| Soonest | 15.05.2007 |
| Latest | 04.04.2023 |
| **Uploaded place** | |
| United States of America | 71 (70.3%) |
| United Kingdom | 13 (12.9%) |
| India | 5 (5.0%) |
| Pakistan | 3 (3.0%) |
| Australia | 3 (3.0%) |
| New Zealand | 2 (2.0%) |
| France | 2 (2.0%) |
| Japan | 1 (1.0%) |
| Nigeria | 1 (1.0%) |
| **Uploader** | |
| Healthcare provider | 24 (23.8%) |
| Non-healthcare provider | 77 (76.2%) |
| **Kind of uploader** | |
| Professional health organization/foundation | 42 (41.6%) |
| Medical journal | 10 (9.9%) |
| Individual, non-medical, without making a profit | 9 (8.9%) |
| Pathologist | 8 (7.9%) |
| Dermatologist | 6 (5.9%) |
| Natural source of healing channel (no financial interest) | 6 (5.9%) |
| Patient | 4 (4%) |
| Private company/hospital/lab | 4 (4%) |
| Pharmaceutical company | 3 (3%) |
| University | 3 (3%) |
| Doctor (not an expert) | 3 (3%) |
| Non-governmental organization | 1 (1%) |
| Individual, non-medical, making a profit | 1 (1%) |
| Hematologist | 1 (1%) |
| Video views | 6.536±15.513 |
| **DISCERN score** | |
| JAMA score | 42.76±16.51 |
| GQS score | 2.10±1.10 |
| Video feedback | 2.51±1.44 |
| Likes | 59.44±172.37 |
| Dislikes | - |
| Comments | 6.89±20.74 |
| Interaction ratio | 1.03±1.28 |
| **Commentary status of videos** | |
| Closed for comments | 36 (35.6%) |
| Open for comments | 65 (64.4%) |
| **Content of videos** | |
| Evidence-based | 76 (75.2%) |
| Not based on evidence | 25 (24.8%) |

GQS: Global Quality Scale, JAMA: Journal of the American Medical Association

**Table 2. Video source and features of groups separated according to DISCERN classification**

| | Group 1, (n = 16) (15.8%) | Group 2, (n = 33) (32.7%) | Group 3, (n = 21) (20.8%) | Group 4, (n = 12) (11.9%) | Group 5, (n = 19) (18.8%) | P* |
|---|---|---|---|---|---|---|
| Professional health organization/foundation | 3 | 11 | 7 | 4 | 17 | |
| Medical journal | 1 | - | 5 | 4 | - | |
| Individual:non-medical, without making a profit | 4 | 4 | 1 | - | - | |
| Natural source of healing channel (no financial interest) | 2 | 2 | 1 | 1 | - | |
| Dermatologist | - | 1 | 2 | 1 | 2 | |
| Pathologist | - | 7 | - | 1 | - | |
| Doctor (not an expert) | 1 | - | 2 | - | - | |
| Private company/hospital/lab | 1 | 2 | 1 | - | - | |
| Pharmaceutical company | 1 | 2 | - | - | - | |
| Patient | 2 | 2 | - | - | - | |
| University | - | 1 | 1 | 1 | - | |
| Non-governmental organization | - | - | 1 | - | - | |
| Individual, non-medical, making a profit | 1 | - | - | - | - | |
| Hematologist | - | 1 | - | - | - | |
| Video time (min.) Mean ± SD | 6.22±6.9 | 8.23±13.1 | 13.31±17.2 | 15.03±20.1 | 45.79±18.1 | < 0.001 |
| Video view Mean ± SD | 11,475±25,585 | 4,593±7,510 | 5,360±12,515 | 11,137±27,069 | 4,146±4,375 | 0.35 |
| Video comment Mean ± SD | 10.38±27.01 | 5.21±9.73 | 11.14±32.64 | 7.83±24.05 | 1.58±3.15 | 0.13 |
| Video like Mean ± SD | 96.00±243.7 | 54.94±121.16 | 86.90±264.74 | 37.25±98.69 | 20.11±39.54 | 0.016 |
| IR Mean ± SD | 1.45±1.73 | 1.33±1.48 | 0.93±0.95 | 0.65±0.70 | 0.48±0.85 | 0.019 |
| **Closed for comments** | | | | | | |
| Yes | 3 | 7 | 7 | 6 | 13 | |
| No | 13 | 26 | 14 | 6 | 6 | |

*Kruskal-Wallis test, IR: Interaction index, SD: Standard deviation, min.: Minute

**Table 3. Evaluation results of video content by video uploaders**

| | DISCERN Mean ± SD (min.-max.) | JAMA Mean ± SD (min.-max.) | GQS Mean ± SD (min.-max.) |
|---|---|---|---|
| Professional health organization/foundation, (n = 42) | 52.07±17.23 (19-75) | 2.69±1.02 (1-4) | 3.24±1.60 (1-5) |
| Medical journal, (n = 10) | 45.10±10.11 (24-58) | 2.40±0.69 (1-3) | 2.40±0.84 (1-4) |
| Individual, non-medical, without making a profit, (n = 9) | 26.89±8.25 (17-43) | 0.67±0.50 (0-1) | 1.33±0.70 (1-3) |
| Natural source of healing (no financial interest), (n = 6) | 34.50±11.64 (25-54) | 1.17±0.75 (0-2) | 2.00±0.89 (1-3) |
| Dermatologist, (n = 6) | 52.00±13.7 (35-69) | 2.50±0.54 (2-3) | 3.33±1.50 (2-5) |
| Pathologist, (n = 8) | 34.13±7.90 (27-52) | 2.00±1.00 (1-3) | 1.88±0.99(1-4) |
| Doctor (not an expert), (n = 3) | 37.33±14.36 (21-48) | 1.67±0.57 (1-2) | 2.33±1.15 (1-3) |
| Private company/hospital/lab, (n = 4) | 30.25±10.65 (18-44) | 1.25±0.95 (0-2) | 1.75±0.95 (1-3) |
| Pharmaceutical company, (n = 3) | 28.00±3.00 (25-31) | 2.00±1.00 (1-3) | 1.33±0.57 (1-2) |
| Patient, (n = 4) | 26.75±5.62 (21-34) | 0.75±0.50 (0-1) | 1.25±0.50 (1-2) |
| University, (n = 3) | 43.67±7.50 (36-51) | 2.67±0.57 (2-3) | 2.67±0.57 (2-3) |
| P* | < 0.001 | < 0.001 | 0.005 |

*Kruskal-Wallis test, SD: Standard deviation, min.: Minimum, max.: Maximum, JAMA: Journal of the American Medical Association, GQS: Global Quality Scale

## Discussion

This study aimed to investigate the suitability of videos as information sources for MF. As a result of the research, the mean DISCERN score for all videos was computed as 42.76 on the DISCERN scale, which is the primary assessment method for determining the information quality of the videos, and it was determined that they were of medium quality. The mean JAMA score was 2.10 (medium reliability), and the GQS score was 2.51 (low-medium quality); both were similar to the overall DISCERN video quality evaluation result. The outcome is relatively high when compared to the findings of many research studies. For example, in a recent study analyzing morphea information on YouTube using DISCERN in dermatology, the average DISCERN score was 32.2 (poor quality).[11]

In another study regarding YouTube eczema treatment information, the mean DISCERN score was 34.6 (poor quality).[12] Salah et al.'s[13] 2022 study, which assessed the quality of YouTube vitiligo information using the DISCERN, GQS, and Accuracy in Digital-Health Instrument scales found that 57% of the videos were of very poor quality and 33% were found to be of poor quality according to the DISCERN scoring system. In contrast, our study found that the mean of all videos was of medium quality, with around 50% being good quality. However, there were also videos with excellent scores in our study. Since MF is a rare skin lymphoma, unlike various diseases such as eczema and acne, this explains why videos on this subject are mainly published by physicians such as dermatologists or hematologists and professional associations. Thus, the content's quality and reliability are higher than that of others, which our study also supports.

The mean DISCERN and GQS scores were of moderate quality, and the JAMA mean score was of low reliability in a study that investigated the usefulness of basal cell carcinoma YouTube videos using DISCERN (modified German version), JAMA, and GQS.[14] In another study, Instagram, one of the social media platforms associated with psoriasis in society, was investigated as a psoriasis information source, and the average DISCERN score was 28.8 (poor quality), emphasizing that Instagram contains lower quality information than other social media platforms, such as YouTube.[15] According to a study exploring 80 videos regarding alopecia areata and androgenic alopecia on TikTok and YouTube, most TikTok video uploaders were female patients who expressed their experiences. Furthermore, healthcare providers had a statistically significant higher DISCERN score on YouTube than patients. Their videos were of high quality according to the DISCERN scoring of healthcare providers, but there was no statistically significant difference observed in the study regarding TikTok.[16]

YouTube is more favorable than TikTok for providing information because there are no time limits on YouTube videos, and viewing videos does not require a subscription. However, the popularity and usage of the TikTok platform have grown recently, leading us to believe that the tendency of experts to share knowledge from YouTube will shift in favor of TikTok as infrastructure improvements, such as video time extension and the growth in the number of users from all segments of society and ages, continue. Today, almost no profession exists that does not use social media, as not using it is almost synonymous with invisibility. Another striking point revealed in the results of our study is the low number of videos uploaded by patients. MF is a disease most commonly seen in middle-aged individuals, with a male-to-female ratio of 2:1, and about 75% of cases are diagnosed after age 50.[17,18] The low use of social media/YouTube in this age range and MF being an infrequent condition may have contributed to this predicament.

Most videos on YouTube about MF contain evidence-based information; however, since MF is a mimicking disease that can easily be confused with common diseases such as eczema, it is often diagnosed late. To help combat this, we believe it would be highly beneficial if dermatologists produced videos to raise awareness of early-stage diagnosis, as video sharing sites have become a popular and valuable way to spread information.

In our study, we also observed that although the videos in group 1 had the lowest DISCERN score, they had the shortest duration, the most likes, and the highest IR, which was statistically significant. This finding indicates that information quality is not the sole factor for reaching a broad audience. Competition on social media platforms such as YouTube is fierce, making garnering high views, and interactions challenging. Health professionals aiming to reach a large audience through their videos should focus on aspects such as high-quality sounds and images, short durations, and eye-catching covering photos and titles. These components capture viewers' attention, boost views, likes, and interactions, and increase the likelihood of a video being promoted on YouTube, ultimately reaching more users.

### Study Limitations

Limitations of our study include the YouTube algorithm differs from person to person, the features YouTube utilizes to rank the most watched videos are unknown, and only English language videos were included.

## Conclusion

We suggest that dermatologists, who have an essential role in the diagnosis and treatment of MF, should be included

in the channels of non-profit professional organizations or medical publications in order to provide accurate information to the public, even if they do not have their own YouTube channels. This will accelerate the advancement of professional organizations currently striving for public knowledge and increase the quality of their content. In conclusion, increasing the volume of content in direct proportion to its quality will ensure that the correct information is more likely to be seen in the YouTube algorithm.

## Ethics

**Ethics Committee Approval:** Not applicable.

**Informed Consent:** Not applicable.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: D.M., G.I.K., S.P.K., Concept: D.M., G.I.K., S.P.K., Design: D.M., G.I.K., S.P.K., Data Collection or Processing: D.M., G.I.K., S.P.K., Analysis or Interpretation: D.M., G.I.K., S.P.K., Literature Search: D.M., G.I.K., S.P.K., Writing: D.M., G.I.K., S.P.K.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

**Financial Disclosure:** The authors declared that this study received no financial support.

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