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]

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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

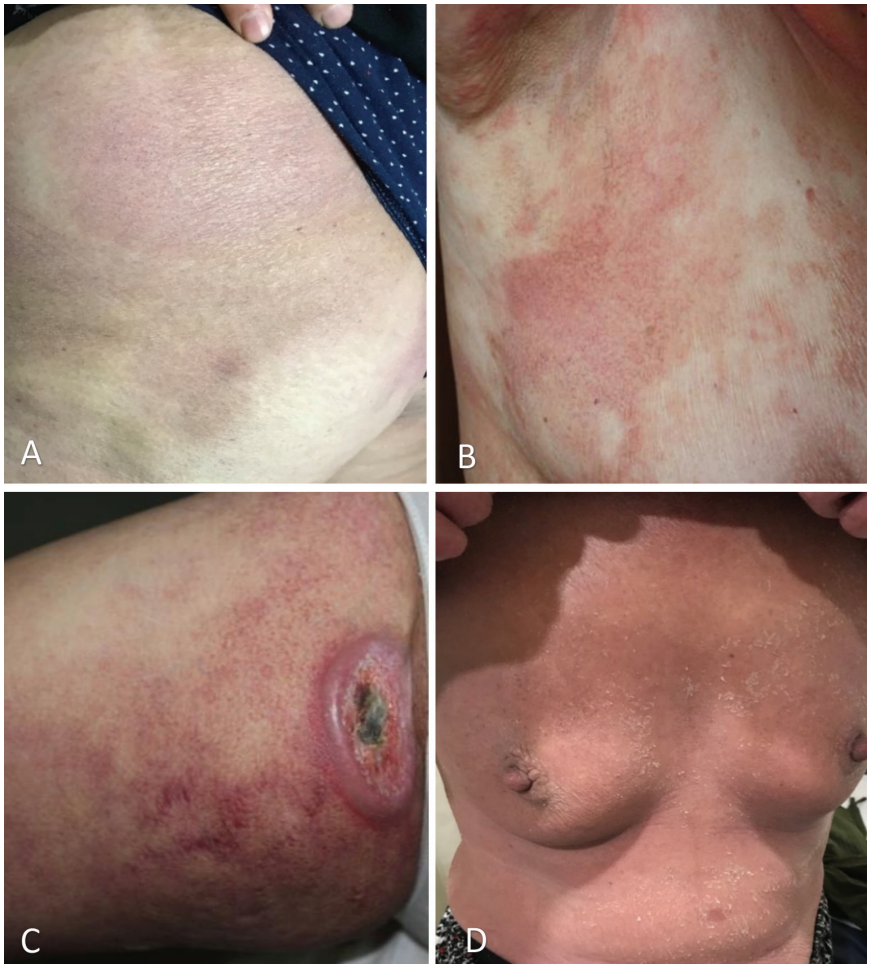

Figure 1. Clinical findings of classical mycosis fungoides: patch on the leg (A); plaques on the right lateral side of the body leg (B); tumor on the right inguinal area (C); and erythroderma (D)

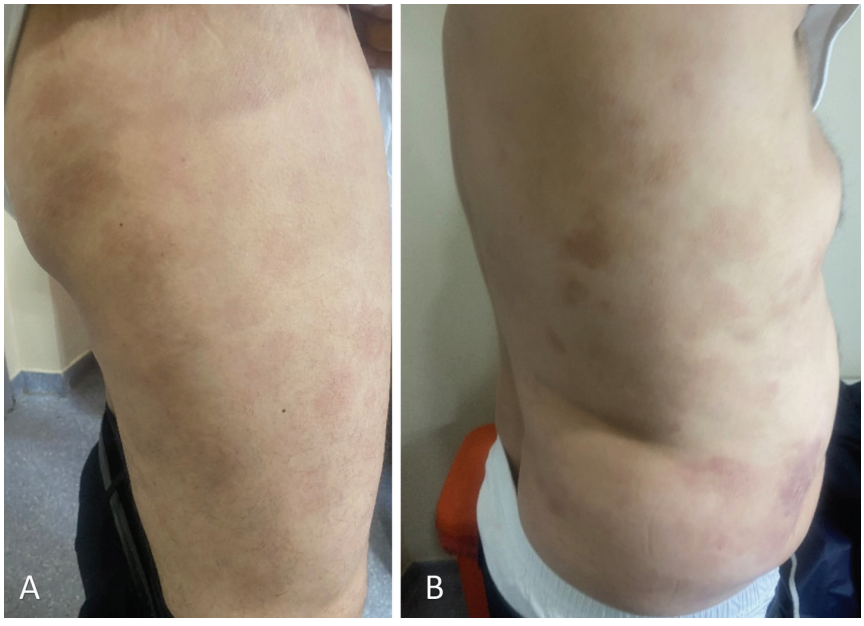

Figure 2. Clinical findings of classical mycosis fungoides: patches on the leg (A); patches and thin plaques on the trunk (B)

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	

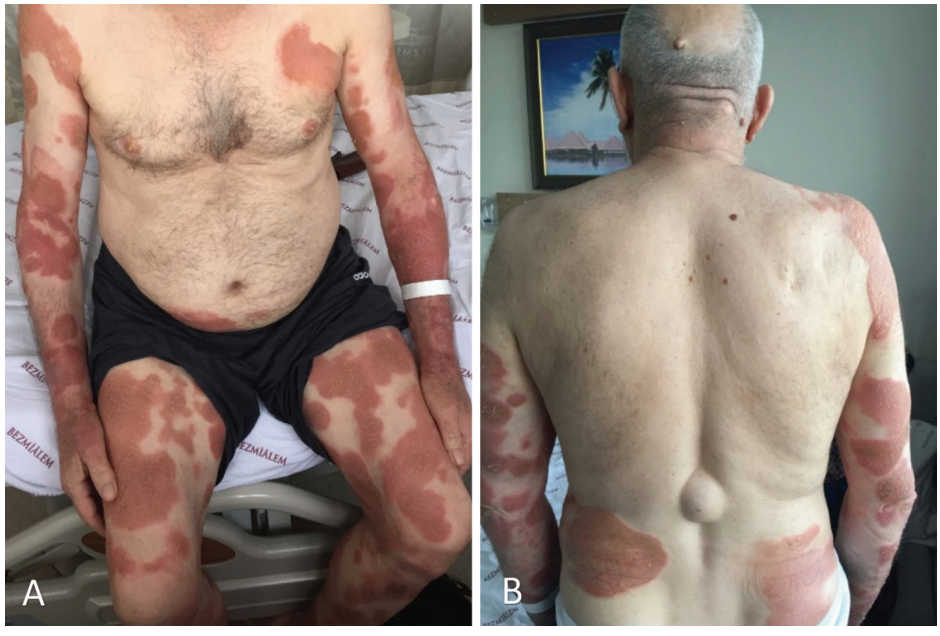

Figure 3. Clinical findings of classical mycosis fungoides: plaques on the anterior surface of the trunk and extremities (A); plaques on the posterior surface of the trunk, hips, and extremities (B)

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]

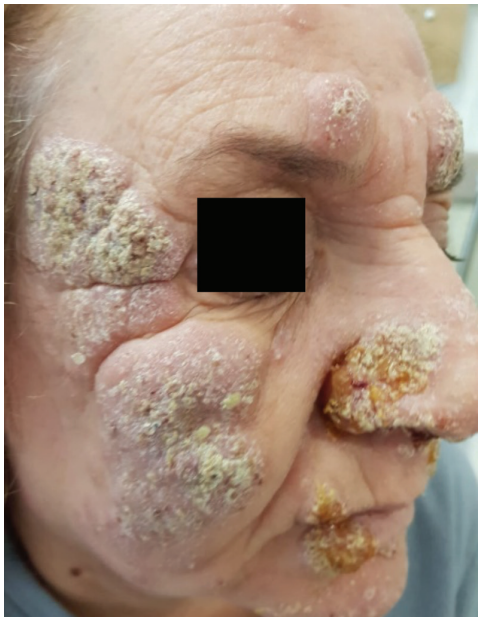

Figure 4. Clinical findings of classical mycosis fungoides: exophytic tumors on the face

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

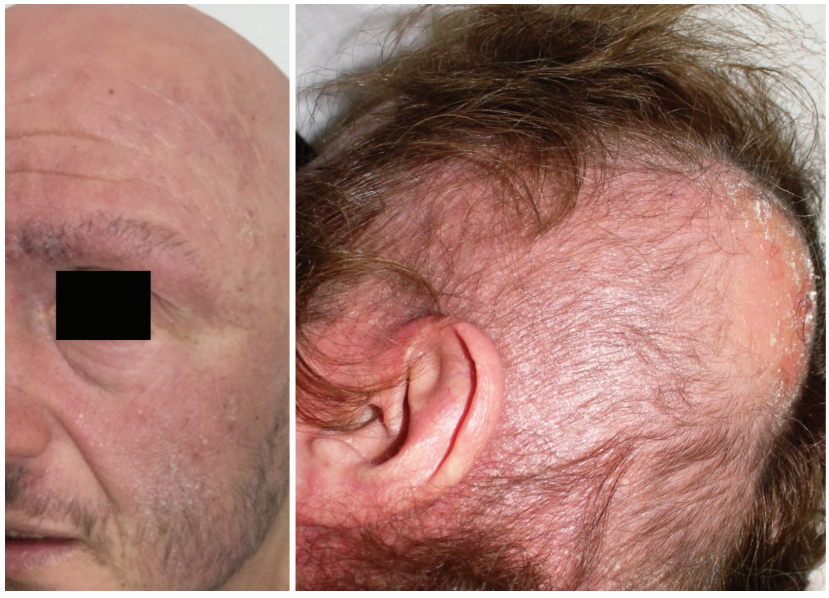

Figure 5. Clinical findings of folliculotropic mycosis fungoides: eyebrow alopecia (A); alopecic patch on the scalp (B)

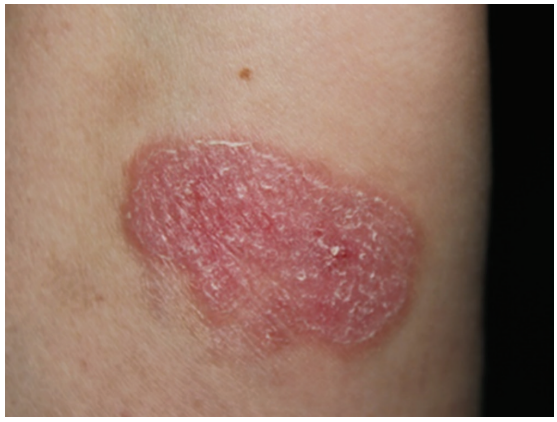

Figure 6. Pagetoid reticulosis (Woringer-Kolopp): erythematous-scale plaque lesion on the upper extremity

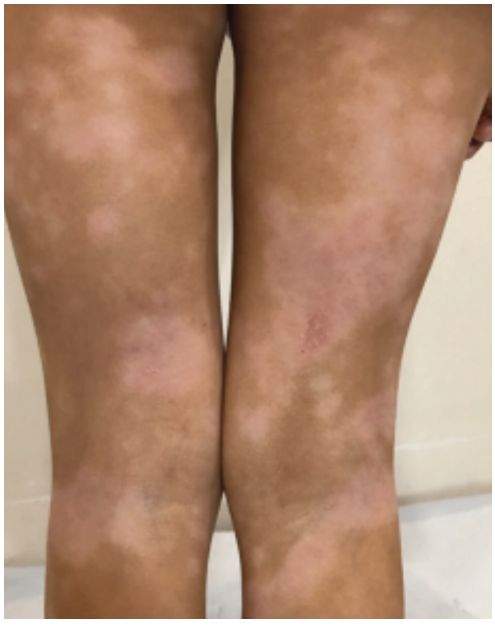

Figure 7. Clinical findings of hypopigmented mycosis fungoides: hypopigmented macules and patches on the lower extremities

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

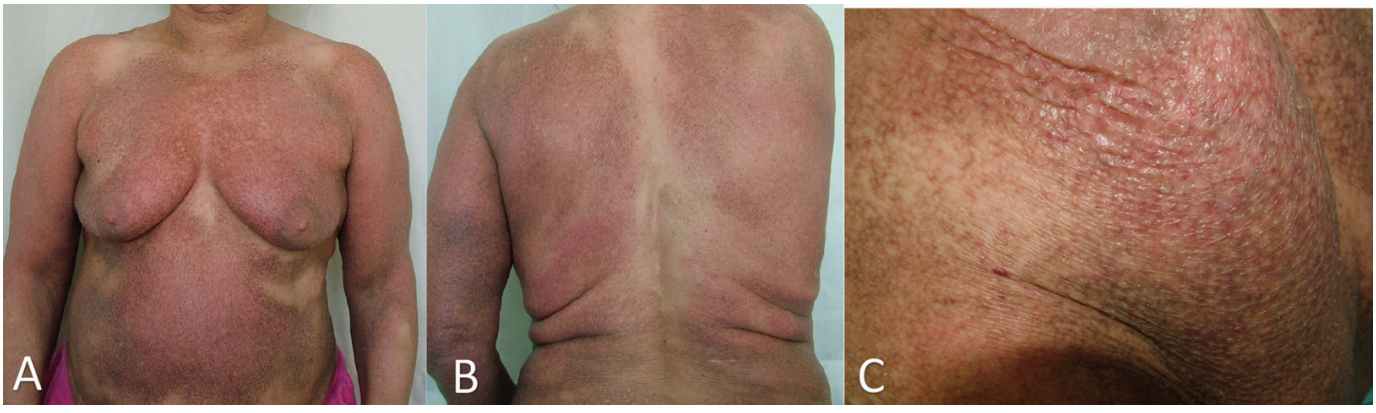

Figure 8. Clinical findings of poikilodermatosis mycosis fungoides: anterior trunk (A), posterior trunk (B), close-up view of poikiloderma (C)

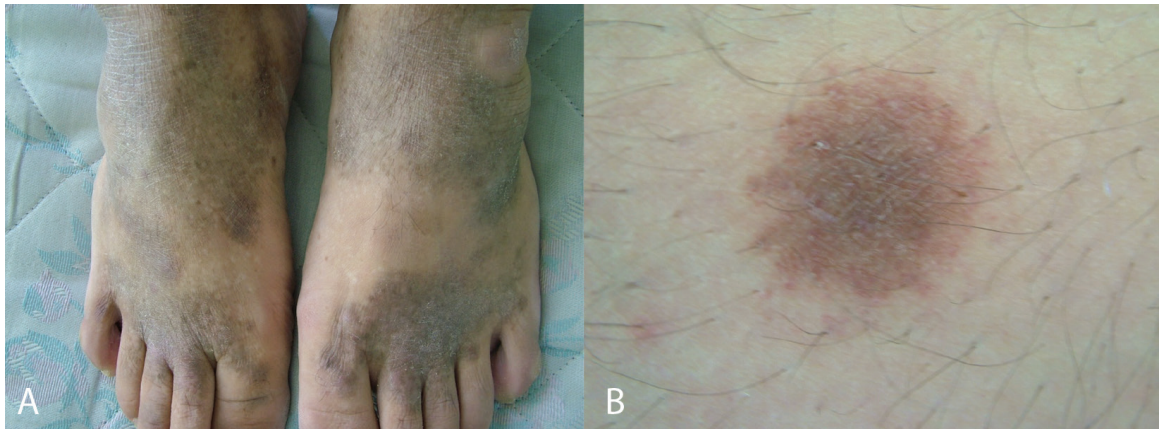

Figure 9. Clinical findings of pigmented purpuric dermatosis-like mycosis fungoides: bilateral lesions on the foot (A), close-up view of a single lesion (B)

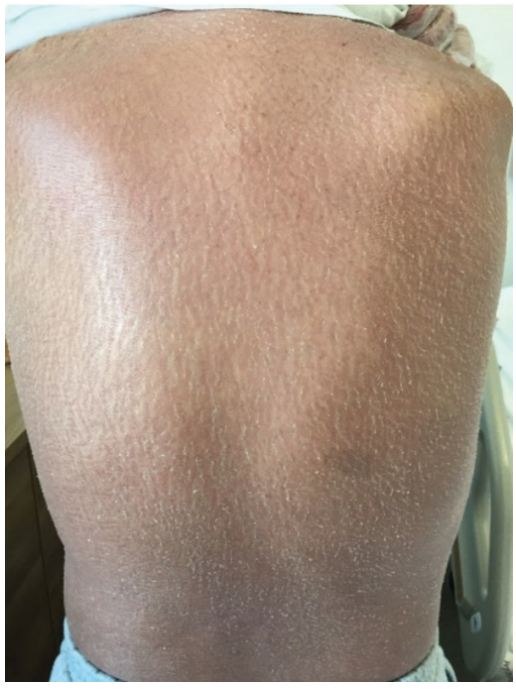

Figure 10. Clinical finding of ichthyosiform mycosis fungoides

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

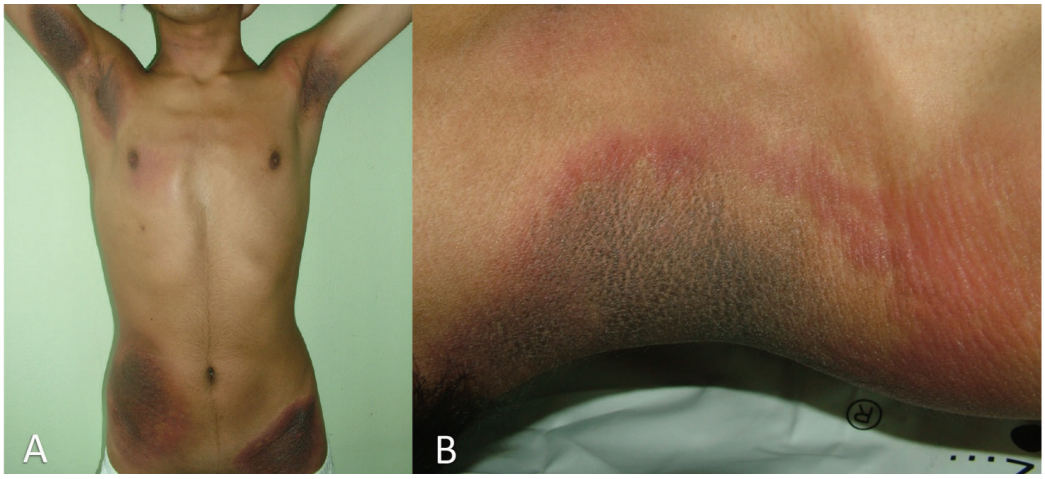

Figure 11. Clinical findings of papillomatous mycosis fungoides: anterior surface of the trunk (A) with an acanthosis nigricans-like lesion in the axillary region

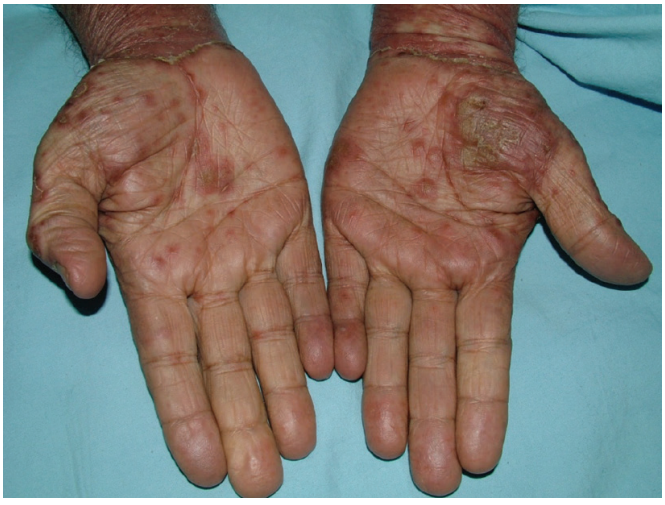

Figure 12. Clinical finding of pustular mycosis fungoides

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

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