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Mycosis fungoides: Review and updates

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Abstract
Mycosis fungoides is the most common type of cutaneous T cell lymphoma. The early diagnosis of MF is still an area of debate and challenging issue due to its resemblance to chronic inflammatory dermatoses. Therefore, MF diagnosis is usually based on clinical-pathological correlation. Different lines of treatment are available for MF according to the disease staging.

Keywords: Mycosis fungoides, T cell lymphoma, lymphomas

Introduction
"It is said that no one truly knows a nation until one has been inside its jails. A nation should not be judged by how it treats its highest citizens, but its lowest ones." - Nelson Mandela
More than 10.2 million people worldwide are held in prisons. As per the World Prison Population List-2013, there is a general trend of growth in prison population in majority of nations, including in India. As of 2017, the latest figures available for India, there are and belong to marginalized or socially disadvantaged groups and have limited knowledge about health and practice unhealthy lifestyles. Thus, they represent a distinct and vulnerable health group needing priority attention [1].

International Law
Mycosis fungoides (MF) is the most common subtype of cutaneous lymphoma, representing about 50% of all lymphomas arising primarily in the skin [1]. It has unclear cause but various hypotheses are proposed. MF results from the malignant transformation of skin-resident effector memory T cells [2, 3].
Clinically, mycosis fungoides is usually associated with a prolonged indolent clinical course where the cases progress through three clinical phases, patch, plaque, and tumor stage [1]. Histopathologically, mycosis fungoides is characterized by an epidermotropic proliferation of small- to medium-sized pleomorphic cerebriform lymphocytes forming intraepidermal collections, so-called Pautrier microabscesses. Different lines of treatment are available for MF according to the disease staging [2].

Mycosis Fungoides
Definition and classification
Primary cutaneous lymphomas represent a heterogeneous group of extranodal non-Hodgkin lymphomas, consisting of cutaneous B-cell lymphoma (CBCL) and cutaneous T-cell lymphoma (CTCL).

Incidence and Epidemiology
The incidence of MF is 6-7 cases/10^6 with marked regional variations [5]. Higher incidence presents in blacks [6]. The disease is more common in adults and elderly patients than children and adolescents, with median age at diagnosis of 55 to 60 years, and a male to female ratio of 2:1 [1]. In children, MF represents the most common type of cutaneous lymphoma [7].

Etiology

Mycosis fungoides is supposed to result from chronic antigenic stimulation that produce uncontrolled clonal expansion and accumulation of T cell helper memory cells in the skin [8]. This is supported by increased numbers of dendritic cells in early MF lesions [9]. Genetic susceptibility and disease initiation or persistence of MF may be due to colonization and relative sensitivity to superantigens in common skin flora. *Staphylococcus aureus* derived alpha-toxin may promote disease progression through positive selection of malignant $CD4^+$ T cells [10]. Specifically, antigen-presenting cell ligands B7 and cluster of differentiation (CD) 40 and their respective T cell costimulatory ligands CD28 and CD40L were detected to be upregulated in MF lesions (11). Serologic evidence for Epsteine Barr virus and cytomegalovirus was found in some MF patients [12].

Immunosuppression and/or immunosuppressive drugs may predispose patients to develop CTCL in rare cases after organ transplantation and in those with HIV [13-15].

Table 1: Classification of primary cutaneous lymphomas by World Health Organization/ European Organization for Research and Treatment of Cancer [4]

Cutaneous B-cell lymphoma	Cutaneous T-cell lymphoma
Indolent clinical behaviour Primary cutaneous marginal zone B-cell lymphoma Primary cutaneous follicle centre lymphoma **Intermediate behaviour** Primary cutaneous diffuse large B-cell lymphoma, leg type	**Indolent clinical behaviour** Mycosis fungoides (and variants) Primary cutaneous CD30+ lymphoproliferative disorder: anaplastic large cell lymphoma Primary cutaneous CD30+ lymphoproliferative disorder: lymphomatoid papulosis Subcutaneous panniculitis-like T-cell lymphoma Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder Primary cutaneous acral CD8+ T-cell lymphomab Hydroa vacciniforme-like lymphoproliferative Disorder
	Aggressive clinical behaviour Sézary syndrome Extranodal natural killer/T-cell lymphoma, nasal type Primary cutaneous aggressive epidermotropic cytotoxic CD8+ T-cell lymphoma Primary cutaneous γ/d T-cell lymphoma Primary cutaneous peripheral T-cell lymphoma, unspecified

Pathogenesis

- **Skin microenvironment**

The skin microenvironment plays an important role in the development of MF which is proposed to arise from a process of chronic inflammation with several immune cells, including dendritic cells, reactive T cells, macrophages, plasma cells, and mast cells [16].

Reactive $CD8^+$ cytotoxic T cells are highly expressed in early MF skin lesions and may have an antitumor response [17]. $FOXP3^+$ regulatory T cells (Treg) have been correlated with improved survival, through suppression of malignant cell proliferation [18] as it was proved to play a role in the suppression of the activity of the neoplastic cells in MF [19]. Both Treg and cytotoxic T cells are significantly downregulated in advanced MF plaque and tumor lesions, these cells lead to systemic immunodeficiency and apoptosis of the surrounding immune cells [20].

Macrophages may secrete chemokines with their immunomodulatory effect that can participate in lymphocyte containment, although macrophages in MF lesions may contribute to tumor growth and disease progression [21, 22]. Tumor-associated macrophages maintain an immuno-suppressive tumor microenvironment by recruiting regulatory T cells (Tregs) and myeloid-derived suppressor cells.

Skin homing of malignant T cells

The skin homing mechanism of malignant T cells is not completely understood, although the role of adhesion molecules and chemokines has been suggested (16). Skin homing T cells isolated from patients with MF and Sézary syndrome express cutaneous lymphocyte antigen and the chemokine receptors CCR-4 and CCR-10, that bind to their specific skin-derived ligands on endothelial cells, keratinocytes, and/or Langerhans cells, so, facilitating migration into the dermis and epidermis [23].

The profile of chemokine receptors differs with disease progression. In tumor stage MF, neoplastic cells increasingly expressing lymphatic homing CCR7, correlating with a loss of epidermotropism and the potential for extracutaneous involvement [24]. Change in cytokine expression profile also occurs with disease progression. Th1 cytokines, interferon gamma.

(IFN-γ), and interleukins (ILs-12 and -2) predominate in early MF. While in advanced stage MF and SS, a shift from Th1 to Th2 cytokines is encountered (25). Th2 cytokines (ILs-4, -5, -10, and -13) are associated with eosinophilia, erythroderma, high levels of immunoglobulin E, immunosuppression, and increased susceptibility to bacterial infections seen in advanced mycosis fungoides and Sézary syndrome [25].

Mycosis fungoides and Sézary syndrome have been shown to arise from different memory T cell subset. Malignant T cells of Sézary syndrome are of the central memory T cell subset with its ability to circulate between skin, lymph nodes, and blood, while those in MF are of non-recirculating resident effector memory T cells [3].

- **Genetic and chromosomal abnormalities**

Mycosis fungoides is caused by an altered immune biology and the accumulation of cytogenetic abnormalities during disease progression, including increased transcription factor activity, such as amplification of JunB Proto-Oncogene, AP-1 Transcription Factor Subunit, that is involved in T-cell proliferation, differentiation, and apoptosis [26]. Constitutive activation of signal transducer and activator of transcription 3 (STAT3) transcription factor is shown in advanced stage MF, while the activation of nuclear factor of activated T

cells and nuclear factor kappa B is maintained throughout the disease in early and advanced stages [27, 28].

- **Dysfunctional apoptosis**

Apoptosis resistance has been detected as a feature in MF. Apoptosis is partially mediated by death receptors, particularly Fas, which is part of the tumor necrosis factor family of receptors. Decreased or defective Fas expression by malignant T cells contributes to advanced/aggressive disease and impaired Fas mediated apoptosis [29-31].

- **Molecular findings**

MicroRNAs are small noncoding RNAs that regulate gene expression. A microarray screen reported that 5 microRNAs (miRs -203, -205, -326, -663, and -711) identify CTCL from benign skin diseases with > 90% accuracy [32].

Clinical presentation

- **Classic mycosis fungoides**

Mycosis fungoides is characterized by a chronic clinical course with slow progression over years and sometimes decades and a clinical morphology compromised of polymorphic patches or plaques in the early stage, and tumors and erythroderma in the more advanced cutaneous stage. Peripheral adenopathy may or may not be present [16, 33]. Patches, plaques and tumors may concomitantly present [1].

Premycotic phase of MF (Para-psoriasis en plaques)

The premycotic phase of MF is the early-phase mycosis fungoides which may be hard to be diagnosed. It is manifested as faint erythematous patches with arcuate geographic borders, greater than 6 cm in diameter, scattered on the proximal extremities and the trunk and show a bathing-suit distribution. Surface of the lesions has faint red-to-salmon color; flaky thin scales; and atrophic, cigarette-paper or tissue-paper. The histopathology of large plaque parapsoriasis reveals a superficial dermal inflammatory infiltrate consists predominantly of lymphocytes which are small and do not show atypical nuclei. Numerous lymphocytes are present along the dermal-epidermal junction and single lymphocytes can be observed in the epidermis. Dilated blood vessels and melanophages can be present. The epidermis shows flattening of the rete ridges when epidermal atrophy is prominent and spongiosis is absent [2].

- **Patch stage MF**

Patches of MF may be generalized or localized, variably large, erythematous pinkish, brownish, or hypochromic lesions with a predilection for sun-protected areas, following the distribution of ‘‘bathing suit’’ areas, including the breasts, buttocks, lower trunk, and groin. Scaling is variable [1]. They resemble psoriasis or parapsoriasis, causing confusions and difficulty with the definition of the early stage of MF [34]. Pruritus is variable from mild to moderate and the lesions may be associated with slight trophy. The patch lesions may remain stable for years before progressing to the plaque stage, undergo remission or indolently progress to plaque stage [35].

- **Plaque stage of classic mycosis fungoides**

Plaques of MF are characterized by being infiltrated, irregular, well demarcated, variably scaling, asymmetrically distributed lesions, annular, polycyclic or horseshoe-shaped configuration. The lesions are erythematous purplish or brownish in color, with more intense pruritus than in the patch stage. In dark skinned patients, patches and plaques tend to appear less erythematous and have greyish or silver hue instead. They may also present on the face and the scalp and occasionally may ulcerate [35].

- **Tumor stage of classic mycosis fungoides**

Tumors of MF may be papular or nodular, solitary or multiple erythematous-purplish lesions. They may progress to large-diameter lesions and may be observed in combination with typical patches and plaques. They prefer the face, the axillary, inguinocrural, inframammary and antecubital regions. When located on the face, they may give lion-like facial aspect. Tumors may grow rapidly in weeks or be stable for months [2, 35].

Lymph nodes or organ dissemination does not occur in the patch stage; it is rare in the plaque stage, but it is frequent in the tumor stage [36, 37]. Regional lymph nodes are the first sites to be affected, and visceral spread may occur in various organs, including spleen, liver and lungs, although the bone marrow is rarely affected [36].

Clinicopathological variants of MF

- **Erythrodermic mycosis fungoides**

Erythrodermic mycosis fungoides is presented with erythroderma and, together with Sézary syndrome, represents erythrodermic CTCL [38]. (Table 2) Erythrodermic MF is considered a progression of MF in the advanced stage and can be differentiated from SS by absent or minimal blood involvement and non-fulfillment of the syndrome's diagnostic criteria. A low level of circulating Sézary cells can be seen in erythrodermic MF [38, 39].

The skin appearance in erythrodermic CTCL may vary from mild erythema to generalized exfoliative erythroderma with keratoderma and fissures on the palms and soles. These cutaneous findings are associated with electrolyte imbalances, hypothermia, hair loss, and eyelid changes/ectropion. The histological and immunophenotypic aspects of erythrodermic CTCL are identical to those of MF, but with less prominent features, such as epidermotropism, Pautrier microabscesses, and haloed lymphocytes. Studies have shown a variable pattern of dermal lymphocytes from superficial perivascular to dense lichenoid infiltrate, suggesting that the features of erythrodermic MF may be more subtle than patch or plaque MF [40].

Table 2: Proposed classification for erythrodermic CTCL and relative hematologic criteria devised by the ISCL in their consensus conference on erythrodermic CTCL [38]

Erythrodermic CTCL	Preexisting MF	Blood findings	Tumor-node-metastasis-blood staging
Sézary syndrome	Rarely	Leukemic	T4, N0-3, M0-1, B2
Erythrodermic MF	Always	Absent or minimal	T4, N0-3, M0-1, B0-1
Erythrodermic CTCL no other specified	Absent	Absent or minimal	T4, N0-3, M0-1, B0-1

B_0: < 5% circulating Sézary cells; B_1: Sézary cell count of < 1000 cells/m3 or < 20% atypical T cells on peripheral smear; B_2: sézary cell count of > 1000 cells/m3 or > 20% atypical T cells on peripheral smear.

- **Follicular/folliculotropic mycosis fungoides**

Folliculotropic MF is the most common variant with characteristic clinical and histological findings and treatment resistance. It has different synonyms including; folliculotropic, follicular, pylotropic, folliculocentric and follicular mucinosis [41]. There is a predilection for male gender in folliculotropic MF [42]. It is presented clinically as erythematous plaques, acneiform lesions, comedones, cysts, milia en plaque, follicular papules, follicular keratosis, papular or alopecic plaques (alopecia mucinosa), including mucin secretion (mucinorrhea) and nodular prurigo-like lesions surrounding hair follicles [43].

The lesions usually prefer the head, neck and upper trunk with typical eyebrow involvement in one third of the cases that show follicular accentuation and possibly alopecia. Associated scarring and alopecia are often seen. Patients with folliculotropic MF suffer from intense pruritus [44]. Histopathologically, there is perifollicular lymphocytic infiltrate that spare epidermis interfollicular space [44]. The follicles classically show corneous plug and follicular destruction with or without mucinous degeneration can also be seen [45].

The prognosis of folliculotropic MF is worse than that of the classic form MF. Folliculotropic MF is considered stage III, regardless of the clinical appearance of the lesion [39, 44, 46].

In folliculotropic MF patients, where treatment is more complicated because skin-directed therapies may fail to reach a depth sufficient to achieve good therapeutic results, Psoralen–ultraviolet A photochemotherapy (PUVA) is usually combined with retinoids. Local radiation therapy is a good option for solitary lesions of folliculotropic MF [2, 47].

- **Pagetoid reticulosis**

Pagetoid reticulosis is a rare lymphoproliferative disorder considered to be a clinicopathologic variant of mycosis fungoides [48]. It is firstly described by Woringer and Kolopp in 1939 [49]. Clinically, pagetoid reticulosis is usually presented with a single, infiltrated, erythematous, slowly-growing plaque with a remarkable hyperkeratotic or psoriatic appearance, located on the distal areas of the extremities [50].

The disease is characterized histopathologically by marked epidermal hyperplasia and proliferation of atypical lymphocytes with marked epidermotropism [50]. Neoplastic lymphocytes may express CD4 or CD8, or may be CD4−/CD8−. Pan-T-cell markers, especially CD7, may be lost and expression of CD30 is variable [51].

- **Granulomatous slack skin**

Granulomatous slack skin is a very rare subtype of MF with a male predominance and usually during adulthood [52] and rarely spread to an extra cutaneous site [42]. Clinically, it is characterized by pendulous folds of skin involve the inguinal and axillary region. As the lesion matures it may become pedunculated [42, 53].

Histologically, granulomatous slack skin shows a dense, diffuse dermal infiltrate of atypical, irregular, convoluted T lymphocytes with cerebriform nuclei and (CD3+, CD4+, and CD8− phenotype) that may extend to the subcutaneous tissue. Additionally, there is diffuse, multinucleated giant cells (~10 nuclei per cell) and macrophages that show prominent elastophagocytosis and lymphophagocytosis, correlating with simultaneous loss of elastic fibers. Molecular analysis reveals a monoclonal rearrangement of the T cell receptor genes [54].

- **Pediatric mycosis fungoides**

Mycosis fungoides comprises approximately 65% of all primary cutaneous lymphomas in pediatric patients. Children may have an indolent clinical course that is difficult to distinguish from inflammatory skin condition with the average time from symptom onset to disease diagnosis is 2-5 years [55]. Pediatric MF may present with classic erythematous patches and plaques with lymphocytic epidermotropism. However, hypopigmented form is overrepresented with >50% of reported pediatric cases describing hypopigmented MF [56]. The lesions can occur on any area of the body but often localize to sun-protected areas. Folliculotropic MF represents the second most common variant of MF in children followed by poikilodermatous MF and hyperpigmented MF that is presented with skin hyperpigmentation, frequently in association with other cutaneous MF lesions [57, 58].

Pediatric mycosis fungoides is characterized by an epidermotropism of lymphocytic infiltrate. The neoplastic lymphocytes in MF typically have a T-helper phenotype ($CD3^+$, $CD4^+$, $CD8^-$) [59]. However, cytotoxic T-cell phenotype ($CD3^+$, $CD8^+$, $CD4^-$) is more frequently seen in children than adults, and the $CD8^+$ variant may be associated with an indolent course [60, 61].

Phototherapy represents the most common treatment modality for pediatric MF with narrowband ultraviolet UVB (NB-UVB) commonly used as the first-line therapy [62].

The prognosis for pediatric MF appears better than adult MF. The majority (~77%) of pediatric patients demonstrate at least partial clearance within 1 y of starting therapy and progression to more advanced disease (stage IIB or higher) is rare [56].

- **Minor variants of classic MF**

Other minor variants of classic MF may appear clinically different but they have overlapping histologic features and a similar clinical course [42]. They are included in table (3) [42].

Table 3: A summary of the minor variants of mycosis fungoides [42]

Variant	Clinical presentation	Histopathology
Hypopigmented mycosis fungoides	Hypopigmented non-atrophic macules and patches [42] More common in children and adolescents and in patients with skin phototype IV-VI [41] Lesions may be isolated or multiple, variable in diameter and sometimes alopecic with usual good response to treatment, but recurrences are common [35, 63]	Epidermotropism and lymphocytic infiltrates in the epidermis [42] Patchy parakeratosis [42] Frequent expression of $CD8^+$ lymphocyte [64] Reduced staining with CD7 is characteristic [65]

	May be the only MF presentation or coexist with plaque lesion or even tumors [35] It is categorized under patch stage of MF and it does not progress beyond patch stage or beyond stage 1B [63] No organ and lymph nodes involvement and no haematological abnormalities [63]	
Granulomatous mycosis fungoides	Hyperkeratotic patches and plaques or poikilodermatous patches [42] Lacks the bulky skin fold characteristic of granulomatous slack skin [42] Papules or ulcerated nodules [66] More common in males aged 50-60 years [66]	Granulomas that resemble sarcoidosis, with multinucleated giant cells [42] Lichenoid lymphocytes with interstitial histiocytes [42] Absence of plasma cells, elastolysis and elastophagocytosis in addition to relative lack of giant cells when compared with granulomatous slack skin [42]
Interstitial mycosis fungoides	Patches and verrucous plaques [42] Acanthosis nigricans like plaques or perioral dermatitis [42]	Infiltration of the dermal interstitium by lymphocytes and few histiocytes dissecting the collagen bundles, resembling the pattern of inflammatory dermatoses, like interstitial granuloma annulare [42] Both epidermotropism and the band-like pattern may be absent, making the diagnosis difficult [67] Most interstitial cells are T lymphocytes with a cytotoxic phenotype in about 50% of the cases [2]
Poikilodermatous mycosis fungoides (poikiloderma atrophicans vasculare)	Typically involves the major flexural areas (breasts, gluteal region and other flexures) and trunk [68] Can be generalized or mixed with other forms of MF [68] Alternating hyperpigmented and hypopigmented, deep-red or brownish plaques with atrophy and telangiectasia [42]	Atrophic flattened epidermis epidermis with epidermotropism [2, 42] Lichenoid infiltrate of neoplastic lymphocytes with basal hydropic degeneration, telangiectatic vessels and macrophages containing melanin in the superficial dermis [2, 41, 42] Immunohistochemical pattern is mainly $CD8^+$ and $CD4^-$ [68]
Syringotropic mycosis fungoides	The lesions may be solitary slightly scaly erythematous brownish plaque, groups of erythematous papules, patches, nodule-like masses and lichenification [2, 41, 69] May be generalized with frequent alopecia and itching [2, 41, 69] Prognosis is similar to that of folliculotropic MF [2]	Prominent involvement of the eccrine glands, often associated with pilotropism in association with syringolymphoid hyperplasia [2, 69] Epidermotropism and Pautrier microabscesses are rare with frequent monoclonal $CD4^+$ lymphocytes [70]
Bullous mycosis fungoides	The average age is 66 years, with men and women affected equally [65] Poor prognosis with mortality within 1 year of diagnosis [65] Vesiculobullous lesions, either flaccid or tense with or without MF typical patches, plaques, and tumors [65] Lesions appear within typical MF lesions or on unaffected skin [65]	Intraepidermal or a subepidermal blister with atypical lymphocytes, epidermotropism, and Pautrier microabscesses [65] Immunohistochemical analysis is consistent with MF [42] Direct and indirect immuno-fluorescence techniques are needed to differentiate bullous MF from other vesiculobullous diseases [42]
Ichthyosiform MF [42]	Widespread ichthyosiform lesions Comedo-like lesions Follicular keratotic papules Common on the extremities	Orthokeratosis of epidermis Thin granular layer Lichenoid epidermotropic infiltrate of small cerebriform lymphocytes and histiocytes
Invisible MF [42]	Few cases only reported in the literature Pruritis NO cutaneous lesion	Perivascular lymphocytic infiltrate Clusters of atypical lymphocytes in the epidermis, with cellular pleomorphism Immunohistochemistry: CD3+, CD4+, CD11a+, CD30-, and CD103- lymphocytes.
MF Palmaris et plantaris [42]	Lesions limited to the palms and/or soles, with possible extension onto the feet, wrists, and fingers Annular and hyperpigmented patches and plaques, tumors, pustules, verrucous changes, ulceration, and nail dystrophy.	Typical classic MF changes

Sézary syndrome

Sézary syndrome (SS) is the aggressive CTCL variant, which is much less common than MF representing 5% of cutaneous T cell lymphomas. It is more common in elderly patients. It is characterized by a triad of: erythroderma with pruritus, lymph nodes enlargement and atypical circulating lymphocytes, referred to as Sézary or Lutzner cells. Associated manifestations may include lagophthalmos, palmoplantar hyperkeratosis, alopecia, and nail dystrophy. Erythroderma may be the result of the progression from previous patches and plaques, idiopathic erythroderma or appearing de novo [41].

The diagnostic criteria for the syndrome are the presence of the circulating monoclonal lymphocyte population which should be identified by molecular or cytogenetic methods with an identity between the circulating T-lymphocyte clone

and the clone presented in the skin, in addition to one of the following criteria:

- At least 1,000 Sézary cells per cubic mm peripheral blood
- An increased population of $CD4^+/CD7^-$ in peripheral blood with remarkable predominance of $CD4^+$ cells in relation to $CD8^+$(CD4/CD8 ratio > 10)
- Sézary cells with a diameter > 14 µm representing > 20% of the circulating lymphocytes
- Loss of T-cell antigen and some markers like CD2, CD3, CD4 and CD5 on flow cytometry [71].

Sézary syndrome is considered separate entity, but in rare cases may follow classic MF [38]. It was previously believed that SS is the leukemic progression of MF, but immunophenotyping and genetic studies support that SS is a separate disease [3]. The typical immunophenotype of Sézary cells is CD3+, CD4+, and CD8−. Aberrant loss of CD7 and CD26 has been found in up to 57% and 86% of cases, respectively. In cases where both CD7 and CD26 lack expression, there is a high sensitivity and specificity for SS [72].

Prognosis of Sézary syndrome is poor, with a mean survival of 2 to 4 years [39]. Both patients of mycosis fungoides and Sézary syndrome patients have an increased liability to develop second malignancy, even second lymphoma. Also, patients with type-B lymphoma may develop type-T MF or Sézary syndrome more frequently than the general population [39].

Histopathology of mycosis fungoides

Mycosis fungoides consists of proliferation of mature $CD4^+$ memory T lymphocytes, with rare cases of $CD8^+$ expression (often associated with hypopigmented MF). The infiltrate consists of predominantly small to intermediate sized atypical lymphocytes with hyperchromatic, cerebriform nuclei surrounded by clear cytoplasm (''haloed'' cells) [2].

- **Histopathology of Patch stage mycosis fungoides**

The histopathologic picture of patch stage MF is characterized by patchy lichenoid or band-like infiltrates of small to medium sized lymphoid cells in the papillary and superficial reticular dermis, mixed with numerous reactive, non-neoplastic lymphocytes and histiocytes, may be distributed a perivascular and interstitial in addition to the band-like manner. It is associated with slight fibrous thickening of the papillary dermis [73, 74]. Papillary dermal fibrosis is one of the key features in the diagnosis of early MF that may lead to a "wiry" collagen appearance [73, 75]. Lymphocytes in the epidermis are usually larger and more pleomorphic than those present in the dermis [65].

Migration of individual pleomorphic lymphocytes with cerebriform nuclei among epidermal keratinocytes, which is described as epidermotropism, is the hallmark of MF. Epidermotropism is present in all cases of MF. It is most prevalent in the patch stage and declined with progression of stage to plaque and tumor stage. Epidermotropism has various morphological aspects including: single intraepidermal cells with no tendency to coalesce, linearly arranged single cells along the basal epidermal layer, pagetoid spread of lymphocytes into the epidermis, tiny collections of three to four lymphocytes, and large intraepidermal clusters of atypical lymphoid cells referred to as Pautrier microabscesses [2, 73, 74].

Basal alignment of lymphocytes along the basal layer of the epidermis has high sensitivity in MF diagnosis and combination of Pautrier's microabscesses and basal lymphocytes correlated significantly with a higher likelihood of MF [73].

An important criterion for MF is the presence of epidermotropism without concomitant epidermal changes. Epidermis in MF patients shows slight hyperkeratosis, usually in the form of elongated mounds of parakeratosis or scale and crusts. Mild to moderate epidermal thickness increases and psoriasiform hyperplasia are seen (42, 74). However, Hyperplastic epidermal changes, including prominent acanthosis and hyperkeratosis, are not typical for MF and should make one consider the possibility of another diagnosis, such as psoriasis vulgaris for example [73, 74].

- **Histopathology of Plaque stage mycosis fungoides**

Plaques of MF reveal a dense, band-like infiltrate of lymphocytes within the upper dermis with significant epidermotropism and presence of Pautrier microabscesses in some cases. Small and/or medium pleomorphic (cerebriform) cells predominate, but some large cells may be observed as well [2]. A small number of eosinophils and plasma cells may be present. The papillary dermis may reveal fibrosis, and epidermal hyperplasia is usually seen [42, 65].

- **Histopathology of Tumor stage mycosis fungoides**

Tumors of MF are characterized by nodular or diffuse deeper, dermal lymphocytic infiltrates with diminished or absent epidermotropism and Pautrier microabscesses. The infiltrate consists mainly of large lymphocytes with pleomorphic and hyperchromatic nuclei and prominent nucleoli involving the entire dermis and often the subcutaneous fat [2, 16, 73]. Typical and atypical mitotic figures are easily identified and make up a larger percentage of the infiltrate [42, 65].

Diagnosis of early stage mycosis fungoides

Early stage mycosis fungoides includes patches and thin plaques of MF with stage IA, IB and IIA according to TNMB classification system, while advanced stage or late stage mycosis fungoides includes stage IIB, IIIA, IIIB, IVA1, IVA2, and IVB [33].

Table 4: Algorithm for diagnosis of early mycosis fungoides proposed by the International Society for Cutaneous Lymphoma [34]

Criteria	Scoring system
Clinical **Basic** Persistent and/or progressive patches/thin plaques **Additional** None sun exposed location Size/shape variation Poikiloderma	2 points for basic criteria plus 2 additional criteria One point for basic criteria plus one additional criterion

Histopathologic **Basic** Superficial lymphoid infiltrate **Additional** Epidermotropism without spongiosis Lymphoid atypia defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours	2 points for basic criteria plus 2 additional criteria One point for basic criteria plus one additional criterion
Molecular Clonal T cell receptor gene rearrangement	One point for clonality
Immunopathologic < 50% CD2+, CD3+, and/or CD5+ T cells < 10% CD7 + T cells Epidermal/dermal discordance of CD2, CD3, CD5, or CD7	One point for ≥1 criterion

A total of 4 points is required for the diagnosis of mycosis fungoides based on any combination of points from the clinical, histopathologic, molecular, and immunopathologic criteria.

- **Transformed mycosis fungoides**

Large cell transformation is characterized by morphologic change of small to medium-sized atypical T cell lymphocytes to a large cell variant. The presence of large lymphocytes > 25% of the total cell population in skin or lymph nodes is considered diagnostic [16, 76]. Large cell transformation is sign of disease progression, but can be the initial presentation of MF. About 1.4% of patients having stage I disease can develop large cell transformation in contrast to 25% and 50% of stage IIB and IV patients, respectively [77]. Although large-cell transformation is observed mostly and classically in tumors of MF, clusters of large lymphocytes may sometimes be found in plaques and rarely even in thin patches of MF [2]. Early diagnosed cases have usually a better prognosis compared to delayed diagnosis [78].

It is recommended to obtain biopsy specimens from patients with established disease MF who develop new papules, plaques, or tumors to exclude large cell transformation [16].

Poor prognostic factors in large cell transformation include:

- Advanced clinical stage at time of transformation [16].
- Early onset of transformation (<2 years from the time of MF diagnosis) [16].
- Extracutaneous sites of transformation [16].
- Elevated beta-2-microglobulin and lactate dehydrogenase [16].
- The percentage of large cells (>25%) doesn't not have any effect on prognosis [16].

Immunophenotyping

Mycosis fungoides is characterized by the presence of cluster of differentiation $CD3^+$ T cell lymphocytes that express a an α/β memory T cell helper phenotype (T-cell receptor [TCR]s+, TCRγ−, CD3+, CD4+, CD5+, CD8−, CD45Ro+, T-cell intracellular antigen [TIA]-1-. Cytotoxic markers such as TIA-1, granzyme B, and perforin are negative in conventional cases of MF, but rare cases express a T cytotoxic phenotype (TCRs+, TCRγ−, CD3+, CD4−, CD5+, CD8+, TIA-1+ or TCRs−, TCRγ+, CD3+, CD4−, CD5+, CD8+/−, TIA-1+) [2]. An elevated CD4:CD8 ratio (≥ 6) is often seen, but normal or decreased ratio does not exclude diagnosis of MF. These cells also express CD45RO, marker of mature memory T cells [16].

The loss of T cell surface antigens, such as CD2, CD5, and CD7, is common phenotypic aberration that may be associated with disease progression (tumor stage). The loss of CD7 in particular is considered a sensitive and specific finding for MF [16]. CD8+ phenotype has been reported more commonly in pediatric MF. Rarely in early MF, and less uncommonly in advanced phases of the disease, an aberrant CD4+/CD8+ or CD4−/ CD8− phenotype can be observed.

In tumor lesions of MF with large-cell transformation, neoplastic T cells may express the CD30 antigen. In addition, lesions of advanced MF may show large numbers of reactive CD20+ B lymphocytes, even forming germinal centers. The prominent B lymphocytes may mask the true T-cell nature of the neoplastic infiltrate, and should not be misinterpreted as a B cell lymphoma.

T cell clonality

The identification of dominant T cell clones in the skin is confirmatory diagnostic test, and is determined by detection of alfa/beta or gamma/ delta TCR gene rearrangements [16]. Clonality has been reported in 40% to 90% of MF cases [16, 79]. Southern blot techniques were used in the past, but recently, polymerase chain reaction using the BIOMED-2 method could detect gene rearrangements with higher sensitivity (80-90%) and specificity (> 90%) [16].

Clonality may be stage dependent and is seen in about 50% of patch, 73% of plaque, and 83% to 100% of tumor MF and erythrodermic MF. Clonality may be difficult to determine in early stage MF. The prognostic significance of clonality is also unclear, particularly in early MF, although the presence of peripheral blood clone in early MF may portend poorer clinical course [80]. The TCR clonality is suggested to be utilized in monitoring treatment response and the detection of residual disease [79, 80]. Additionally, detection of the same clone in multiple skin and/or lymph node biopsy specimens is more commonly associated with progressive disease of mycosis fungoides than identification of oligoclonal or multiclonal T cell populations [81].

Staging of mycosis fungoides

Staging investigations should include a computed tomography (CT) scan of the neck, chest, abdomen and pelvis in all patients with CTCL, with the exception of those with early stages of MF unless there is palpable lymphadenopathy [82]. Recommended evaluation/initial staging of the patient with mycosis fungoides is shown in table (5) [39].

Table 5: Recommended evaluation/initial staging of the patient with mycosis fungoides [39]

Complete physical examination including Determination of type(s) of skin lesions: If only patch/plaque disease or erythroderma, then estimate percentage of body surface area involved and note any ulceration of lesions. If tumors are present, determine total number of lesions, aggregate volume, largest size lesion, and regions of the body involved. Identification of any palpable lymph node, especially those ≥ 1.5 cm in largest diameter or firm, irregular, clustered, or fixed. Identification of any organomegaly.
Skin biopsy Most indurated area if only one biopsy. Immunophenotyping to include at least the following markers: CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20. CD30 may also be indicated in cases where lymphomatoid papulosis, anaplastic lymphoma, or large-cell transformation is considered. Evaluation for clonality of TCR gene rearrangement.
Blood tests CBC with manual differential, liver function tests, LDH, comprehensive chemistries. TCR gene rearrangement and relatedness to any clone in skin. Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including CD4+/CD7- or CD4+/CD26-).
Radiologic tests In patients with T1N0B0 stage disease who are otherwise healthy and without complaints directed to a specific organ system, and in selected patients with T2N0B0 disease with limited skin involvement, radiologic studies may be limited to a chest X-ray or ultrasound of the peripheral nodal groups to corroborate absence of adenopathy.
Lymph node biopsy Excisional biopsy is indicated in those patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered, or fixed.

The TNMB classification system (Tables 6 and 7) [39] is the most widely used means for classifying the extent of and stage patients with mycosis fungoides and Sézary syndrome [39]. Overall, the TNMB classification and clinical staging system has provided clinically useful prognostic information and has been widely used for treatment selection and stratification in clinical trials [39, 83].

Table 6: ISCL/EORTC revision to the classification of mycosis fungoides [39]

TNMB stages	
Skin	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface. May further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥ 10% of the skin surface. May further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumors (≥ 1-cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes §; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 *
N_{1a}	Clone negative#
N_{1b}	Clone positive#
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2
N_{2a}	Clone negative#
N_{2b}	Clone positive#
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells **
B0a	Clone negative#
B0b	Clone positive#
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative#
B1b	Clone positive#
B2	High blood tumor burden: ≥ 1000/μL Sézary cells per mm3 with positive clone#

*For node, the Dutch histopathological classification of lymph node involvement is supported by the ISCL/EORTC. Grade 1: dermatopathic lymphadenopathy, Grade 2: dermatopathic lymphadenopathy; early involvement by MF (presence of cerebriform nuclei > 7.5 μm), Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells, Grade 4: complete effacement

**For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumor burden for B_2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded $CD4^+$ or $CD3^+$ cells with CD4/CD8 ratio of 10 or more, (2) expanded $CD4^+$ cells with abnormal immunophenotype including loss of CD7 or CD26.

#A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

Table 7: Staging of mycosis fungoides [39]

Stage	T	N	M	B
IA	1	0	0	0 or 1
IB	2	0	0	0 or 1
IIA	1 or 2	1 or 2	0	0 or 1
IIB	3	0 or 2	0	0 or 1
III	4	0 or 2	0	0 or 1
IIIA	4	0 or 2	0	0
IIIB	4	0 or 2	0	1
IVA1	1 or 4	0 or 2	0	2
IVA2	1 or 4	3	0	0 or 2
IVB	1 or 4	0 or 3	1	0 or 2

Prognosis

For early-stage disease, male sex, age (≥ 60 years), presence of plaques (T1b/T2b), histological evidence of folliculotropic disease and palpable or histologically confirmed dermatopathic peripheral nodes (N1/Nx) are adverse factors for progression and survival [84].

For advanced or late MF disease, four independent prognostic factors are identified, namely age > 60 years, large cell transformation in skin, raised lactate dehydrogenase and stage IV disease [85]. Patients with stage IIB disease have a poor prognosis, and prognosis of patients with stage III erythrodermic MF, without evidence of lymph node or peripheral blood involvement, is broadly similar to that for stage IIB MF [33].

Treatment of mycosis fungoides

Selection of appropriate treatment is based on the stage of disease [33].

a. Skin-directed treatment

- **Topical therapies**

Although topical therapies have some clinical efficacy for patches and thin plaques (Stage IA–IIA MF). There is no evidence to suggest that topical therapies have a significant impact on the course of the disease for advanced stages of MF, although SDT can relieve skin symptoms such as pain and pruritus [33].

- **Topical corticosteroids**

Topical corticosteroids, especially class 1 (very potent) compounds, are effective for patches and plaques in some patients with early-stage IA/IB MF, but responses are rarely complete [33].

- **Topical mechlorethamine (nitrogen mustard)**

Nitrogen mustard is an effective topical therapy for early-stage MF [33]. It is used in a concentration of 0.02% ointment or gel preparation [86]. When combined with betamethasone cream, 0.02% aqueous solution of mechlorethamine, twice weekly for 6 months, better responses was reported [87]. Irritant contact dermatitis is the most common side effect depending on the preparation used [33].

- **Topical carmustine**

Topical carmustine is suggested to have a similar efficacy to mechlorethamine [88]. However, it carries the risk of bone marrow suppression due to extensive absorption. The incidence of irritant contact dermatitis is lower than mechlorethamine (10%) [33].

- **Topical bexarotene**

Topical bexarotene (1% gel) has been shown to be effective for refractory or persistent, early stage MF [89]. Irritant contact dermatitis is common [33].

- **Other topical therapies**

Imiquimod 5% cream, 5-fluorouracil cream, topical retinoid preparations (tazarotene 0.1%, tretinoin 0.1%) and tacrolimus 0.1% ointment showed efficacy in early stages of MF (90-93).

- **Phototherapy**

Phototherapy is the standard treatment in patients with early stages of MF (Stage IA–IIA) who are not controlled by topical therapy. Repeated courses may be considered (33).

Patients with tumors (Stage IIB MF) who have coexisting patches and plaques may benefit from phototherapy. Patients with erythrodermic MF are often intolerant of phototherapy monotherapy due to aggravation of pruritus [33].

Both NB-UVB: (TL-01: 311–313 nm) and broadband UVB (290– 320 nm) phototherapy can produce better response in patients who have only patches (94). NB-UVB is as effective as PUVA for treatment of early-stage disease, with no difference in time to relapse (95). UVB could induce high response rates, including a number of complete responses, in children with the hypopigmented MF (96). The used regimen of NB-UVB in various studies, two to three times weekly for 12–14 weeks (33).

High-dose UVA1 phototherapy: (340–400 nm), which penetrates more deeply than both UVB and UVA is also effective (97).

PUVA is effective with high complete response rates in early stages. The recommended regimens is, PUVA, twice weekly for 12–14 weeks (98). Maintenance PUVA was given to almost all responding patients (99). However, maintenance PUVA therapy does not prevent future relapse and the risks may outweigh the benefits (100).

PUVA can often be used as a salvage therapy, as in relapse in patients with advanced disease (Stage IVA2–B MF) (33).

PUVA combined with interferon-alpha, bexarotene or retinoids (acitretin) does not improve overall response but may improve duration of response and can the reduce cumulative UVA dose. In contrast, combination PUVA regimens are rarely indicated as first-line therapy for tumor or nodal disease, but are often utilized as an adjuvant or salvage therapy for patients with persistent disease following debulking treatment for cutaneous tumors or

nodal/visceral disease [33].
The undesirable side effects of PUVA include chronic photodamage and secondary skin cancers [101].
Excimer laser appears to be safe, effective and well tolerated for patches, but its accurate therapeutic role remains to be established [102].
Photodynamic therapy has been reported as a safe and well tolerated treatment for solitary plaques which are resistant to topical treatment [33].

- **Radiotherapy (localized radiotherapy)**

Mycosis fungoides is a highly radiosensitive malignancy, and localized radiotherapy remains an effective treatment for patients with all stages of disease [103, 104]. The dose-fractionation regimen should take into account the size of the treatment area, the treatment site and potential risk of acute and late damage to adjacent organs. It is appropriate to use the minimum dose of radiotherapy to obtain local control [105].
Total skin electron beam therapy is a highly effective treatment for MF with excellent complete response rates for all stages [103].
Total skin electron beam therapy adverse effects include significant toxicity, fatigue, erythema and desquamation, alopecia, lower-leg oedema, blisters and skin infection [106].

b. Systemic treatment

- **Systemic biological therapies**
- **Interferon-alpha**

Interferon-alpha is used in all stages of pretreated MF, with variable dose schedules (3–9 megaunits, three to seven times weekly). Response rates are higher in early stages of disease [33].

- **Retinoids and rexinoids**

Acitretin, a retinoic acid receptor retinoids, have mild effects in early stages of MF as monotherapy, but in combination with PUVA they may reduce the cumulative UVA dose and time to response, and improve duration of response [33].
Bexarotene, a retinoid X receptor rexinoid, have shown significant efficacy and good duration of response with low rates of disease progression in early-stage disease [107]. Bexarotene is licensed for the treatment of late-stage MF refractory to at least one systemic agent, particularly for erythrodermic disease, but monotherapy is unlikely to be effective for tumors or nodal disease [108].

- **Antibody therapies**

  At present, there is no evidence that antibody therapies should be used for patients with early-stage disease.
- Alemtuzumab is administered intravenously at the standard dose of 30 mg three times per week with high overall response and complete remission rates, but typically responses are short lived, with only a minority of patients achieving responses for longer than 12 months [109, 110].
- Brentuximab vedotin is an antibody–drug conjugate comprised of an anti-CD30 monoclonal antibody attached by an enzyme-cleavable linker to the antimicrotubule agent, monomethyl auristatin E, which is released upon internalization into CD30-expressing tumor cells [111].

Denileukin Diftitox

Denileukin diftitox is a genetically engineered fusion protein combining the full-length sequence of human IL-2 with the cytotoxic and membrane-translocating domains of the diphtheria toxin. After binding to the IL-2 receptor (IL-2R) on neoplastic T cells, the drug is internalized. Denileukin diftitox is FDA but not EMA approved for MF, Toxicity includes hypersensitivity reactions and vascular leak [112].

- **Other approved biologic therapy for MF include**

  Bortezomib, Romidepsin and Vorinostat both are Histone deacetylase inhibitors for the treatment of refractory, progressive, persistent, or recurrent CTCL [33].

- **Chemotherapy**

Systemic chemotherapy is usually reserved for patients with advanced disease, or disease refractory to SDT or immunobiological therapy, and is palliative rather than curative. Chemotherapy is contraindicated for early stages of disease, as low-grade disease is relatively resistant to chemotherapy and response duration is short [33].

The most reported regimen used in MF is CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).

Extracorporeal photopheresis

Extracorporeal photopheresis is an FDA approved treatment for mycosis fungoides and Sézary syndrome. In contrast, there is a lack of evidence for use of extracorporeal photopheresis in stage IVA2–B MF. It is not effective for stage IIB MF. There is no evidence to suggest that extracorporeal photopheresis should be used for patients with early-stage disease [113].

- **Histone deacetylase inhibitors**

Histone deacetylase inhibitors are an emerging class of drugs that increase acetylation of histones and nonhistone proteins affecting gene transcription, which results in cell-cycle arrest and apoptosis. Histone deacetylase inhibitors should not be used for early-stage MF but can be effective for patients resistant or refractory to SDT [114].

- **Autologous or allogeneic peripheral blood or bone marrow stem cell transplant**

Autologous haemopoietic stem cell transplant appears to be associated with only short-term remission and is therefore difficult to justify [115]. In contrast, allogeneic autologous haemopoietic stem cell transplant is a complex form of immunotherapy aimed at consolidating treatment of advanced and refractory MF to produce a durable complete remission [116]. Reduced intensity allogeneic stem cell transplantation regimen that included Total skin electron beam irradiation or fludarabine/melphalan prior to transplant is widely used due to its ability to induce complete remissions and lower risk of toxicity and sepsis [117].

Conclusions

Mycosis fungoides is an indolent common CTCL with a higher incidence in adults and elderly patients. Different clinical variants are recognized with the common histopathological findings being the epidermotropism of

small- to medium-sized T lymphocytes which is characterized by cerebriform nuclei and T-helper phenotype. Diagnosis of MF is based on combination of the clinical, histopathologic, molecular, and immunopathologic findings. Treatment of MF differ according to staging. Early stage MF usually responds to skin directed therapy, while advanced stage MF requires systemic lines with more aggressive therapies.

Conflict of Interest

Not available

Financial Support

Not available

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