Mycosis fungoides—clinical and histopathologic features, differential diagnosis, and treatment

Lorenzo Cerroni, MD

Abstract

Mycosis fungoides (MF) is the most common type of cutaneous lymphoma. The term MF should be used only for the classical presentation of the disease characterized by the evolution of patches, plaques, and tumors or for variants showing a similar clinical course. MF is divided into 3 clinical phases: patch, plaque, and tumor stage, and the clinical course is usually protracted over years or decades. Histopathologically, MF is characterized by an epidermotropic infiltrate of T lymphocytes that displays in most cases a helper phenotype. Cytotoxic variants are well described and do not have specific clinical, histopathological, or prognostic features. MF should be differentiated from other cutaneous epidermotropic lymphomas and from many inflammatory dermatoses with some similar clinicopathological features. The therapy of MF is planned mainly according to the stage and extent of the disease. In early phases, nonaggressive options represent the first-line strategy (eg, local corticosteroids, psoralen, and ultraviolet A [UV-A] irradiation, etc.). In patients with advanced disease, good results with potential for cure have been obtained with allogeneic stem cell transplantation, but toxicity is a serious limiting factor for this treatment. Conventional systemic chemotherapy and single-agent chemotherapy (eg, gemcitabine) give usually good results in advanced MF, but recurrences are the rule. Monoclonal antibodies directed against cluster of differentiation (CD)52 (alemtuzumab), CD30 (brentuximab vedotin), and chemokine receptor 4 (CCR4; mogamulizumab), as well as several other experimental therapies, have shown promising results and represent a valid alternative.

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Mycosis fungoides (MF) is the most common type of cutaneous lymphoma, representing almost 50% of all lymphomas arising primarily in the skin.[1-3] It is defined as an epidermotropic, primary cutaneous T-cell lymphoma (CTCL) composed of small- to medium-sized T lymphocytes with cerebriform nuclei and with a T-helper phenotype (but cytotoxic variants are not uncommon). The term MF should be used only for the classical presentation of the disease characterized by the evolution of patches, plaques, and tumors or for variants showing a similar clinical course. The incidence of MF is 6-7 cases/10,[6] with marked regional variations[4] and with a higher incidence in blacks.[5] The disease is more common in adults and elderly patients with a male to female ratio of 2:1,[2,3] but it can be observed in children and adolescents as well, and in this age group, too, it represents the most common type of cutaneous lymphoma.[6] The etiology of MF is unknown. Association with chronic skin disorders and with long-term exposure to various allergens has been observed in some cases, and a genetic predisposition may play a role in others. No convincing link to viral infections has been demonstrated so far. MF has been observed in patients who received solid organ transplantation, suggesting that immune suppression may contribute to the development of the disease.

MF is divided into 3 clinical phases: patch, plaque, and tumor stage, and the clinical course is usually protracted over years or decades. It is estimated that over 90% of patients with early MF do not progress to tumor stage and do not show extracutaneous manifestations of the disease in their lifetime.[1-3,7]

Clinical features

Clinically, MF presents with patches, plaques, or tumors or a combination of them.[1] Although patches are considered a clinical feature of early MF, it should be underlined that they are frequently seen admixed with plaques and tumors in patients with advanced disease and that patients with advanced MF who are in complete remission may relapse with patches, plaques, or tumors. Patches of MF are characterized by generalized or localized, variably large, erythematous lesions with a predilection for sun-protected areas, particularly the buttocks and the breast in women (Figures 1 and 2). Scaling is variable, depending also in part on previous treatment. Plaques of MF are characterized by infiltrated, irregular, variably scaling, erythematous, or reddish-brown lesions (Figure 3).

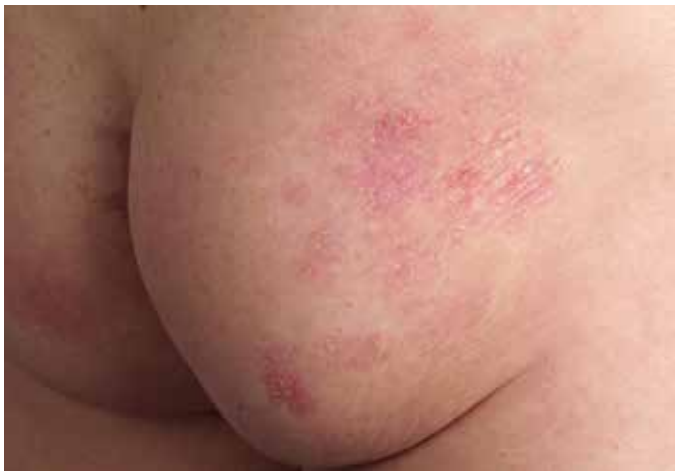

FIGURE 1. Localized patches of MF. Flat, partly scaly, erythematous lesions restricted to the sun-protected area of the buttocks. MF, mycosis fungoides.

Research Unit Dermatopathology, Medical University of Graz, Graz, Austria
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Correspondence: Lorenzo Cerroni, MD; lorenzo.cerroni@medunigraz.at

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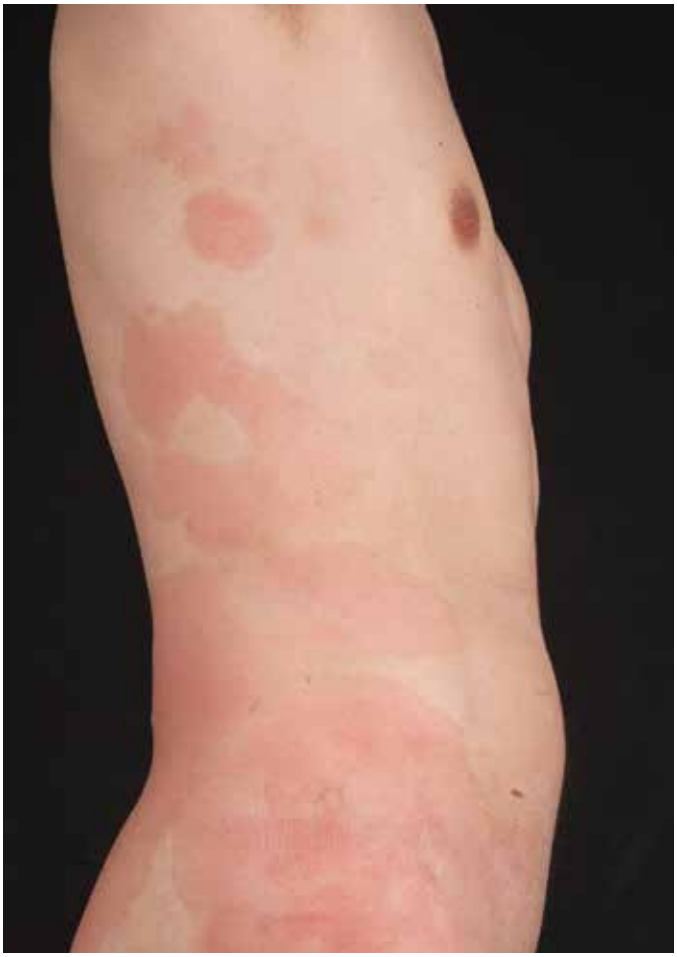
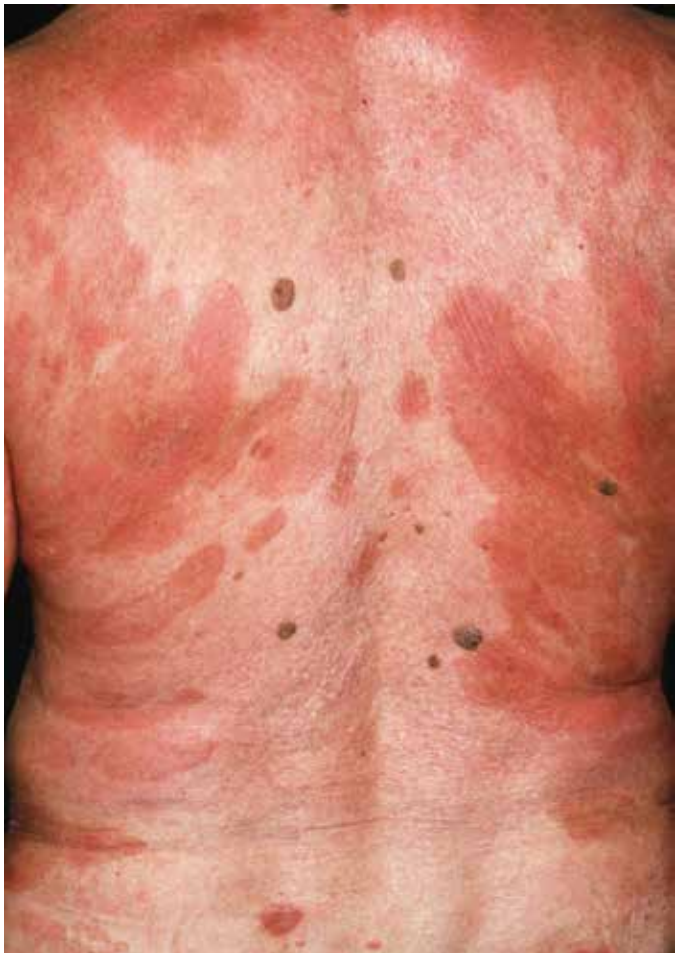


■ **FIGURE 2.** Generalized patches of MF. Flat erythematous lesions on the trunk. MF, mycosis fungoides.



■ **FIGURE 3.** Plaques of MF. Erythematous patches and flat plaques on the trunk. MF, mycosis fungoides.

Typical patches are usually observed contiguous to plaques or at other sites of the body. Plaques of MF should be distinguished from flat tumors of the disease. In patients with dark skin, patches and plaques of MF appear less erythematous and have a greyish or silver hue instead. Tumors in MF may be solitary, localized, or generalized and may be observed in combination with typical patches and plaques or in the absence of other lesions (Figures 4 and 5). Ulceration is common. The growth rate of tumors in MF is variable: they may grow rapidly in a matter of weeks or be relatively stable for months. Partial regression is not uncommon. Involvement of the mucosal regions in patients with MF is unusual in early phases but may be observed in advanced stages. Erythroderma may develop in patients with MF and should be distinguished from Sezary syndrome (Figure 6). In fact, although in the recent past (and even today) MF and Sezary syndrome were included together in a generic group of CTCLs, they are considered as separate entities in the WHO classification, display different molecular features, have a different prognosis, and should be managed differently.

Histopathological and immunhistochemical features

Histopathologically, MF is characterized by an epidermotropic proliferation of small- to medium-sized pleomorphic lymphocytes ("cerebriform") forming intraepidermal collections (so-called "Pautrier's microabscesses"; Figure 7). Although these "microabscesses" are considered to be the histopathological hallmark of the disease, they may be absent in early lesions, particularly in biopsies taken under treatment, and are commonly absent in tumors as well. It should also be emphasized that, although histopathologic criteria for the diagnosis of early MF are available, in many cases a definitive diagnosis can be made only upon careful clinicopathological correlation. In addition, several histopathologic patterns have been described in early MF, many of them similar to those observed in inflammatory dermatoses, thus underlying the difficulties in the histopathologic diagnosis of the disease.[8]

Early lesions of MF reveal, in the vast majority of cases, a patchy lichenoid or band-like infiltrate in a fibrotic papillary dermis. Small lymphocytes predominate. Epidermotropism of solitary lymphocytes is usually found, but Pautrier's microabscesses are uncommon. The presence of "halo" lymphocytes (lymphocytes with slightly larger nuclei surrounded by a small halo), of lymphocytes aligned along the basal layer of the epidermis ("basilar epidermotropism"; Figure 8), and of many intraepidermal lymphocytes in areas with only scant spongiosis ("disproportionate" epidermotropism; Figure 9) represent useful clues. Unusual histo-

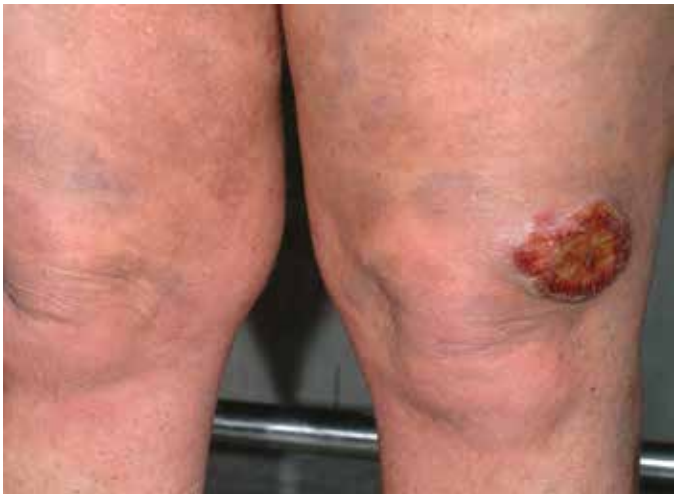


FIGURE 4. Tumor of MF. Ulcerated tumor on the distal part of the thigh. Note partly regressed flat lesions of the disease on both legs. MF, mycosis fungoides.

pathologic patterns in early phases of MF include (1) the presence of prominent spongiosis, (2) interface alteration, sometimes with several necrotic keratinocytes similar to the picture of erythema multiforme, (3) marked pigment incontinence with melanophages in the papillary dermis, (4) extravasation of erythrocytes simulating the picture of lichen aureus, and (5) marked dermal edema, among others. A pattern characterized by a flattened epidermis with a lichenoid infiltrate and dilated vessels in the papillary dermis is the histopathological counterpart of poikilodermatous MF.

Plaques of MF are characterized by a dense, band-like infiltrate of lymphocytes within the upper dermis with epidermotropism and presence of Pautrier's microabscesses in some cases (Figure 10A and 10B). Cytomorphologically, small and/or medium pleomorphic (cerebriform) cells predominate, but some large cells may be observed as well.

Tumors of MF are characterized by nodular or diffuse infiltrates involving the entire dermis and often the subcutaneous fat (Figure 11A and 11B). Angiocentricity and angiodestruction may be present rarely, mimicking the picture of natural killer (NK)/T-cell cytotoxic lymphomas, and prominent involvement of the subcutaneous fat may mimic a subcutaneous panniculitis-like T-cell lymphoma. In this context, it should be remembered that tumors of MF are morphologically indistinguishable from those of other types of primary or secondary cutaneous NK/T-cell lymphoma. In advanced stages of MF, large lymphocytes (immunoblasts, large pleomorphic cells, or large anaplastic cells) may become prominent within the neoplastic infiltrate (Figure 11B). Large-cell transformation is defined as the presence of large lymphocytes exceeding 25% of the infiltrate or of large lymphocytes arranged in nodules.[9-11] Although large-cell transformation is observed mostly in tumors of MF, clusters of large lymphocytes may sometimes be found in plaques and rarely even in thin patches of MF.

The neoplastic lymphocytes of MF usually show an α/ß memory T-helper phenotype (T-cell receptor [TCR]ß$^+$, TCRγ$^-$, cluster of differentiation [CD]3$^+$, CD4$^+$, CD5$^+$, CD8$^-$, CD45Ro$^+$, T-cell intracellular antigen [TIA]-1$^-$; Figure 10B). In tumoral lesions, there

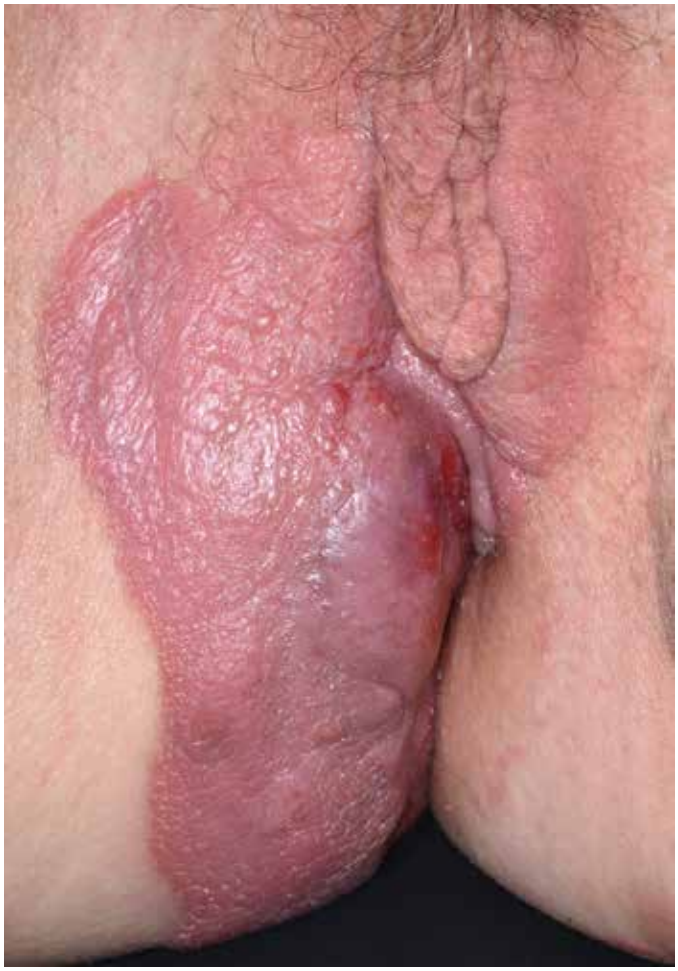


FIGURE 5. Tumor of MF. Large, confluent, tumoral inguinal lesion with focal ulceration. MF, mycosis fungoides.

may be loss of pan-T-cell antigens (CD2, CD3, CD5). Cytotoxic markers such as TIA-1, granzyme B, and perforin are negative in conventional cases of MF, but a minority of cases exhibiting a T-cytotoxic phenotype exist (TCRß$^+$, TCRγ$^-$, CD3$^+$, CD4$^-$, CD5$^+$, CD8$^+$, TIA-1$^+$ or TCRß$^-$, TCRγ$^+$, CD3$^+$, CD4$^-$, CD5$^+$, CD8$^{+/-}$, TIA-1$^+$).[12] A 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 addition, biopsies of tumor lesions may reveal expression of cytotoxic proteins in cases that previously were negative.[13] CD56 positivity has also been observed rarely in biopsies of otherwise conventional MF. There are no clinical and/or prognostic differences between cases with helper or cytotoxic phenotype.[14,15] However, in cases with cytotoxic phenotype, correlation with the clinical features is crucial in order to exclude other cytotoxic lymphomas such as cutaneous aggressive epidermotropic CD8$^+$ cytotoxic T-cell lymphoma, cutaneous γ/δ T-cell lymphoma, or cytotoxic lymphomatoid papulosis. It should also be remembered that variable phenotypic features can be observed in different biopsies of MF taken from one patient within a short period of time.[16]

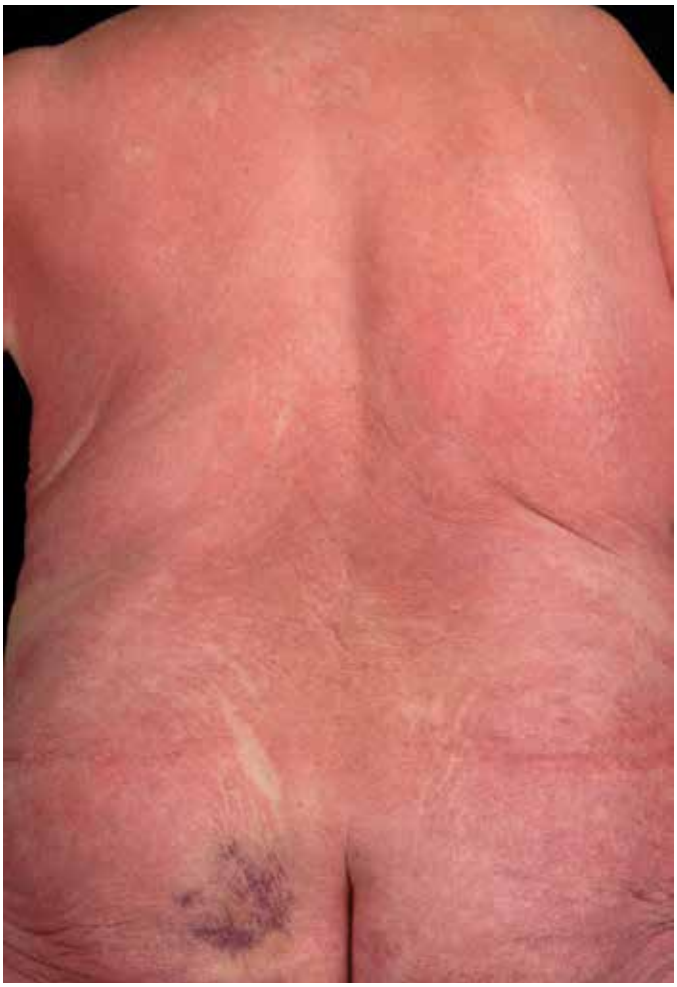


FIGURE 6. Erythrodermic MF. Infiltrated erythematous lesions covering >90% of the body. MF, mycosis fungoides.

Staining for programmed cell death protein (PD)-1 is positive in a proportion of cases of MF, and some cases showing the complete phenotype of T follicular helper lymphocytes (TFH) cells (PD-1$^+$, B-cell lymphoma [Bcl]-6$^+$, chemokine ligand [CXCL]13$^+$, CD10$^+$) have been described.[17]

Langerhans cells and other dendritic cells are increased in number in early stages of MF, sometimes mimicking a Langerhans cell histiocytosis. In rare cases, intraepidermal clusters of Langerhans cells may simulate Pautrier's microabscesses, but these cells are positive for CD1a rather than CD3. Such cases may be difficult to distinguish from lesions of lymphomatoid contact dermatitis.

Particularly in tumor lesions of MF with large-cell transformation, neoplastic T cells may express the CD30 antigen. In patients with known MF, a diagnosis of anaplastic large-cell lymphoma or lymphomatoid papulosis in tumors with large-cell morphology and CD30 expression should be considered only upon compelling evidence.[18] In this context, most cases of MF are negative for IRF4 translocations, whereas primary cutaneous large-cell anaplastic lymphomas are positive.

In exceptional cases, an aberrant expression of the B-cell antigen CD20 by neoplastic T lymphocytes can be observed. In addition,

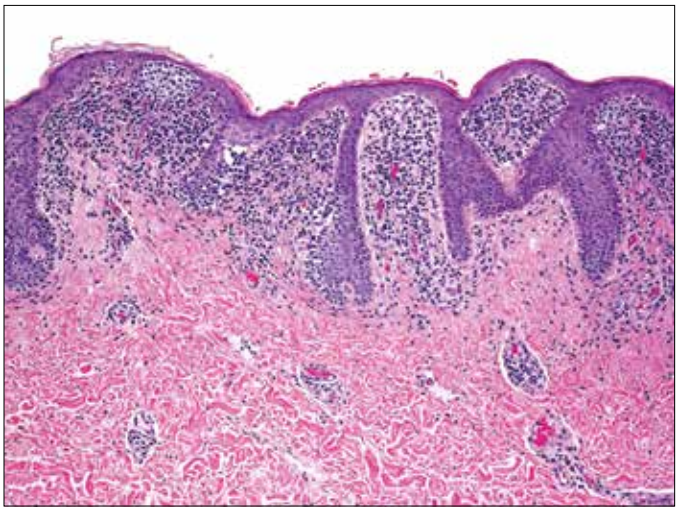


FIGURE 7. Patch of MF, histopathological features. Band-like infiltrate with many intraepithelial lymphocytes and "Pautrier's microabscesses." MF, mycosis fungoides.

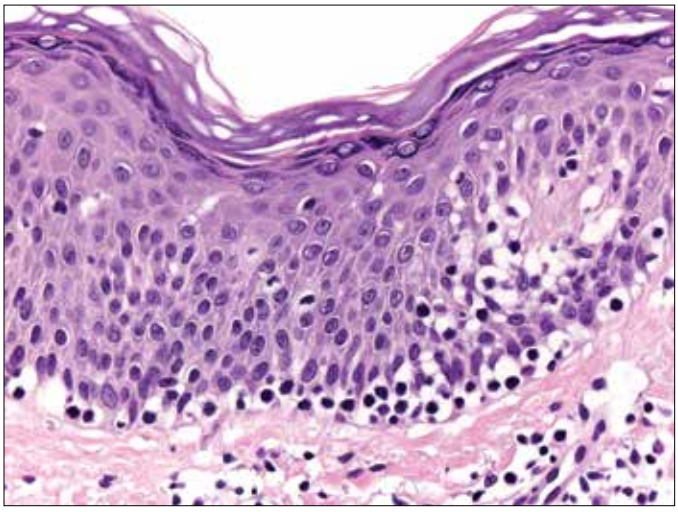


FIGURE 8. Patch of MF, histopathological features. "Basilar" epidermotropism characterized by many intraepithelial lymphocytes aligned along the basal layer of the epidermis. MF, mycosis fungoides.

lesions of advanced MF may show large numbers of reactive CD20$^+$ B lymphocytes, even forming germinal centers. The prominent B lymphocytes may be prominent and mask the true T-cell nature of the neoplastic infiltrate, and should not be misinterpreted as a B-cell lymphoma. In this context, it must be emphasized that cases of cutaneous composite lymphoma have been described (composite lymphomas are characterized by lesions showing histopathological features of 2 distinct lymphomas in one and the same biopsy); in the skin, the 2 lymphomas are mostly MF and B-cell chronic lymphocytic leukemia.

Molecular features

The TCR genes are clonally rearranged in the majority of cases of MF, but the percentage of positive cases depends on the selected

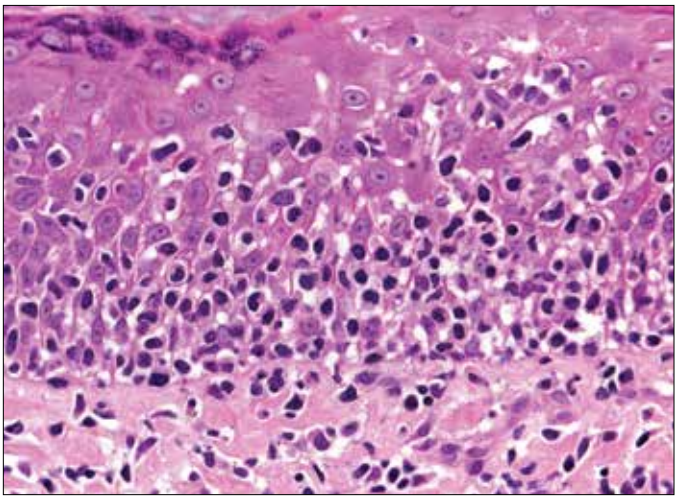


FIGURE 9. Patch of MF, histopathological features. "Disproportionate" epidermotropism characterized by many intraepithelial lymphocytes but only scant spongiosis. MF, mycosis fungoides.

method.[19] TCR sequencing increases the sensitivity and specificity of TCR analysis and better characterizes the neoplastic clones.[20-22]

Somatic mutations can be observed in different components of the TCR signaling pathway, in T^H2 differentiation-related genes, in genes allowing to circumvent the growth suppression mediated by transforming growth factor beta (TGF-β), and in genes that confer resistance to apoptosis mediated by tumor necrosis factor receptor superfamily (TNFRSF).[23-27] Activating Janus kinase 3 (JAK3) mutations, as observed in a recent study, may be targeted by specific drugs.[27] Constitutive activation of *STAT3* and inactivation of *CDKN2A/p16INK4a* and *PTEN* may be associated with disease progression.[28]

Clinicopathological variants

Besides conventional presentations, several variants of MF have been described. Three variants were included separately in the WHO European Organization of Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous lymphomas[2] and are also mentioned in the 2017 revision of the WHO classification of tumors of hematopoietic and lymphoid tissues,[3] namely, folliculotropic (pilotropic) MF (FMF), localized pagetoid reticulosis (Woringer-Kolopp), and granulomatous slack skin. These variants will be discussed in detail in the article by Willemze also in this issue. However, discussed below will be a few variants not considered distinct enough from conventional MF to warrant their own categories but still with some differences and not discussed in the article by Willemze.

Parapsoriasis en plaques

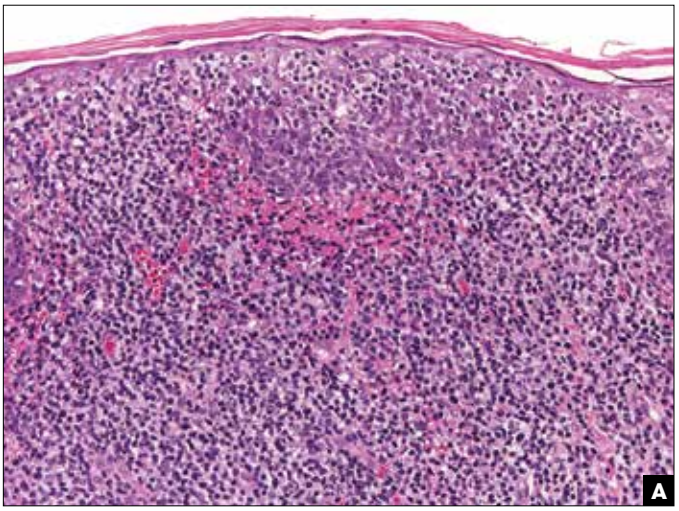
The exact nosology of the so-called "parapsoriasis" and its relationship to MF are yet unclear.[29] Although progression of small-patch parapsoriasis (SPP) to more advanced stages of MF can occur, most patients with SPP experience an indolent course with remissions and relapses but without progression, and the management should be nonaggressive. On the other hand, large-patch parapsoriasis is clinically and histopathologically indistinguishable from MF, and in my opinion, it represents an early manifestation of the disease.

Syringotropic MF

Syringotropic MF (SMF) is a rare variant of the disease with many overlapping features with FMF (Figure 12).[30] It is characterized by a prominent involvement of the eccrine glands, often associated with pilotropism (Figure 13). The lesions may be solitary or, more commonly, generalized, and prognosis seems to be similar to that of FMF.

Interstitial MF

Interstitial MF is a variant of MF characterized histopathologically by dermal infiltrates of lymphocytes dissecting the collagen bundles, mimicking the pattern of inflammatory dermatoses such as interstitial granuloma annulare, inflammatory stage of local-



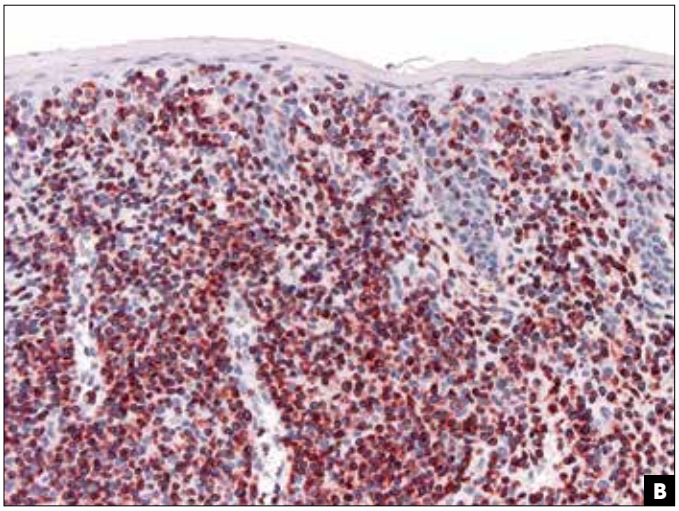
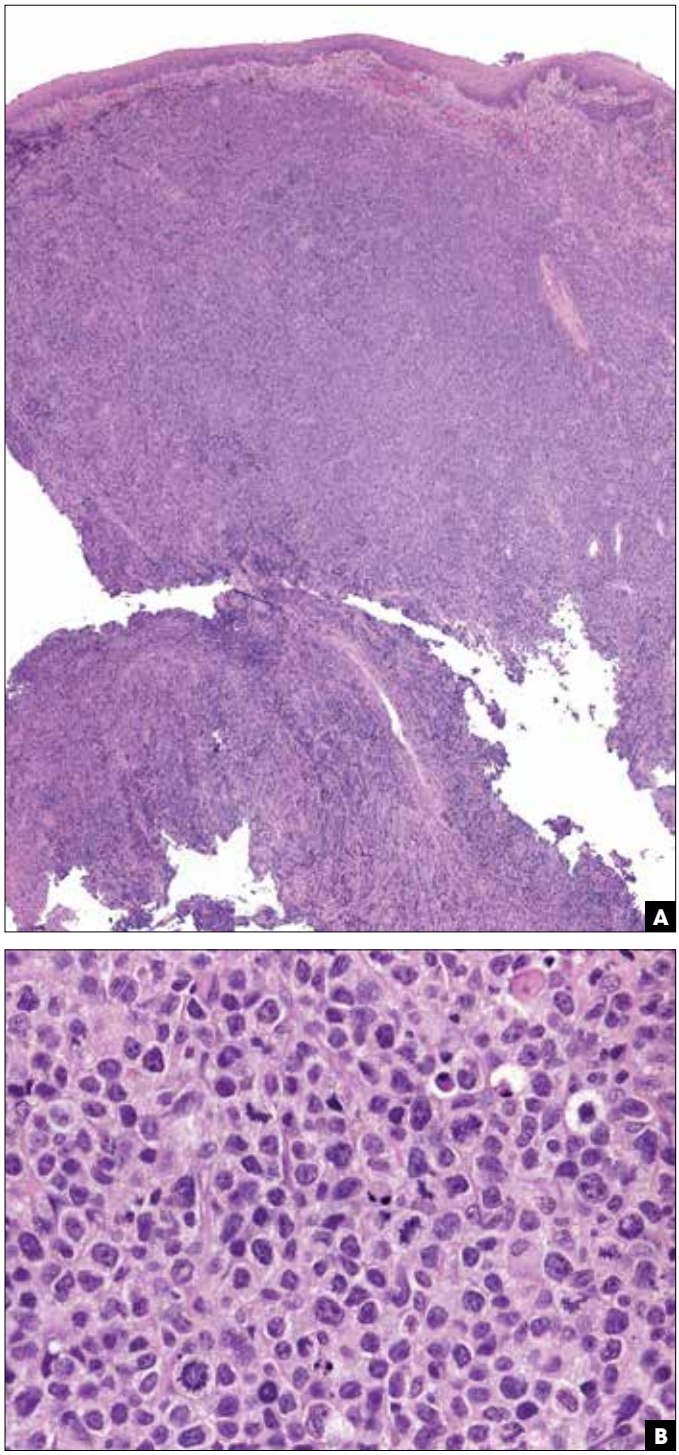


FIGURE 10. Plaque of MF, histopathological features. **(A)** Dense epidermotropic infiltrate with "Pautrier's microabscesses"; **(B)** Staining for CD3 highlights the intraepidermal lymphocytes. MF, mycosis fungoides.

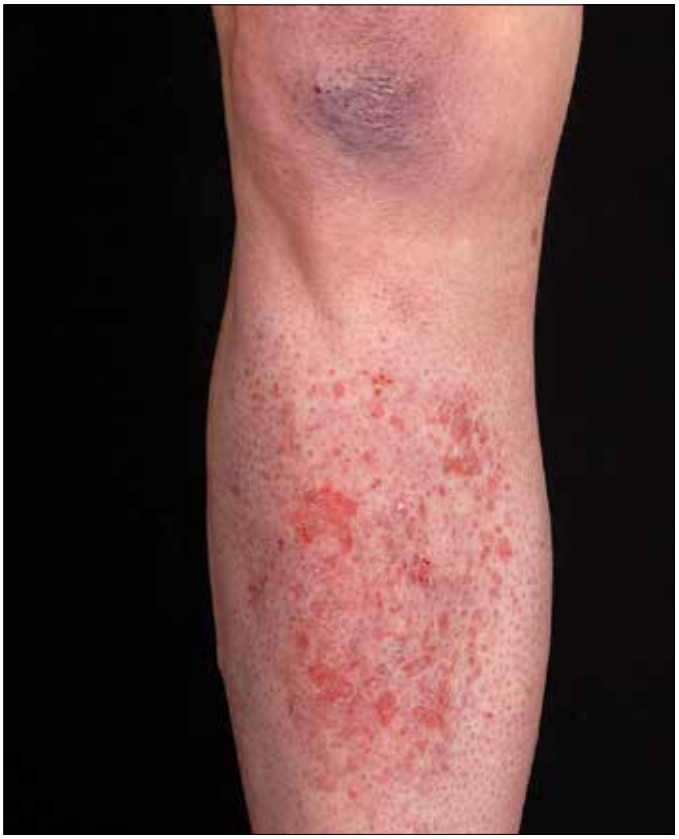
ized scleroderma, and interstitial granulomatous dermatitis (Figure 14).[31] It is observed usually in flat tumors of MF without specific clinical features. Both epidermotropism and a band-like pattern may be missing, thus representing a diagnostic pitfall. Some collagen fibers are surrounded by neoplastic lymphocytes, resembling the "rosetting" observed in interstitial granulomatous dermatitis (in this pattern of inflammatory dermatoses, however, the fibers are surrounded by histiocytes). Immunohistology shows that most interstitial cells are T lymphocytes, in about half of the cases with a cytotoxic phenotype. It should be remembered that granuloma annulare may rarely present with pseudolymphomatous infiltrates and that genuine granuloma annulare has been reported in a patient with MF.



■ **FIGURE 11.** Tumor of MF, histopathological features. **(A)** Dense, diffuse lymphoid infiltrates without involvement of the epidermis; **(B)** Cytomorphology shows that large, pleomorphic cells predominate (large-cell transformation). MF, mycosis fungoides.

Differential diagnosis

MF should be differentiated from benign and malignant conditions that may present with similar clinicopathologic features. Several lymphomas may show epidermotropic infiltrates, including cutaneous γ/δT-cell lymphoma, cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, lymphomatoid papulosis, cutaneous anaplastic large-cell lymphoma, cutaneous manifestations of extranodal NK/T-cell lymphoma, nasal-type, Sezary syndrome, and adult T-cell leukemia/lymphoma (ATLL), among others.[32] In fact, epidermotropic infiltrates can be observed rarely even in B-cell lymphomas. As a rule, cutaneous infiltrates characterized by prominent epidermotropism should be the subject of accurate phenotypic analyses, including also in situ hybridization for Epstein-Barr virus. In countries endemic for human T-lymphotropic virus (HTLV-I), a diagnosis of MF should be accepted only if an



■ **FIGURE 12.** SMF. Partly pilotropic, partly erosive, long-standing lesions on the knee and lower leg. SMF, syringotropic mycosis fungoides.

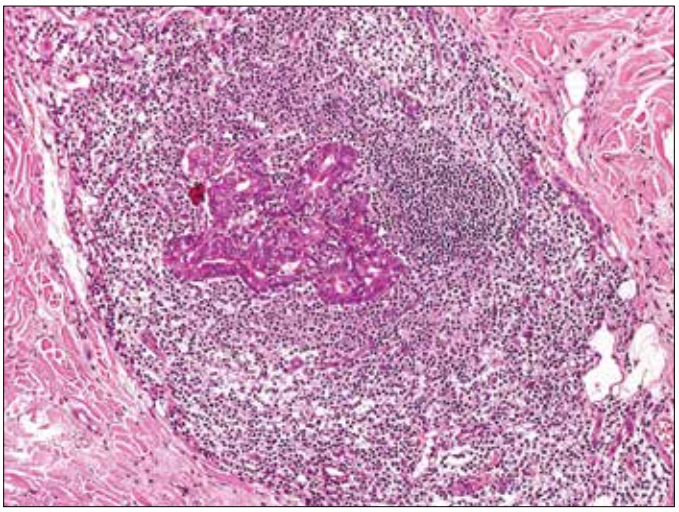


FIGURE 13. SMF, histopathological features. Dense lymphoid infiltrates surrounding and infiltrating eccrine structures characterized by syringometaplasia. SMF, syringotropic mycosis fungoides.

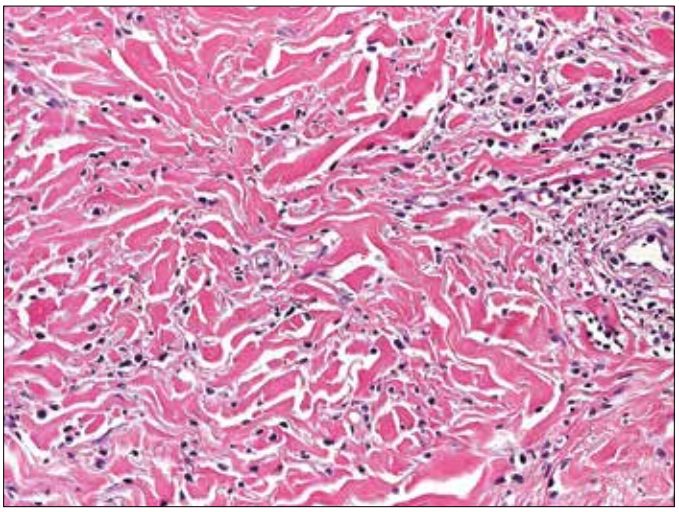


FIGURE 14. Interstitial MF, histopathological features. Lymphocytes arranged as solitary units or small cords splaying the dermal collagen bundles. MF, mycosis fungoides.

infection with HTLV-I can be excluded because cutaneous manifestations of ATLL are clinically and histopathologically indistinguishable from those of MF. Careful history taking and accurate correlation with the clinical picture is necessary in order to exclude MF in cases of cutaneous cytotoxic lymphoma.

MF should also be distinguished from several benign inflammatory conditions, including lichenoid keratosis, lymphomatoid eczematous dermatitis, lymphomatoid drug eruptions, and the inflammatory stage of lichen sclerosus, among many other. In this context, it should be underlined that a diagnosis of solitary MF, besides the clinicopathologic setting of localized pagetoid reticulosis, should be accepted only in cases with compelling evidence. The histopathologic diagnosis of early MF may be extremely difficult, and correlation with the clinical picture is crucial in order to make a definitive diagnosis. On the other hand, in many cases of early MF, "nonspecific" histopathologic features may be observed in a given specimen, often due to long periods of treatment before the biopsy is done ("therapy-resistant" dermatitis). It should also be remembered that marked epidermotropism and Pautrier's microabscesses, the two histopathological features of the disease most valuable for diagnosis, are absent in the majority of specimens of early MF. Immunohistologic features of early MF are not distinctive and are similar to those observed in many inflammatory skin conditions. It has been suggested that loss of expression of the T-cell–associated antigen CD7 represents a helpful clue, but in my opinion, this finding is of limited relevance, and T lymphocytes in some cases of benign inflammatory conditions can also show partial loss of CD7.

Molecular analysis of TCR gene rearrangement may be helpful in the differentiation of MF from benign skin conditions. Detection of the same clone in lesions from different skin sites suggests MF rather than an inflammatory disorder. TCR sequencing allows better characterization of the T-cell infiltrate and is superior to conventional polymerase chain reaction studies in the analysis of clonality. On the other hand, TCR sequencing studies have shown that neoplastic cells in some lesions of MF may be as few as 10% of the entire population of T lymphocytes,[22] thus providing an explanation for the difficulties encountered in the histopathological assessment of these cases.

Treatment

The therapy of MF is planned mainly according to the stage and extent of the disease.[33-37] The revised staging classification proposed by the International Society for Cutaneous Lymphomas (ISCL) is used in most centers in order to plan treatment properly.[38] Most of the new treatment modalities that have been recently introduced target the advanced stages of the disease. Because MF is a low-grade cutaneous lymphoma with prolonged survival, the efficacy of new treatment modalities should be evaluated according to standardized end points and response criteria in order to compare different studies and treatment modalities. A consensus statement of the EORTC, ISCL, and United States Cutaneous Lymphoma Consortium defined complete response in the skin as 100% clearance of skin lesions, partial response as 50%-99% clearance without new tumors, stable disease as <25% to <50% clearance in skin disease without new tumors, and progressive disease as ≥25% increase in skin disease or new tumors.[39] Several end points have been identified and defined precisely, including objective response rate, time to response, response duration, time to relapse or freedom from relapse, time to treatment failure or freedom from treatment failure, time to progression, progression-free survival, disease-free survival, and relapse-free survival.

For the early phases of MF, which may last for several years or decades, nonaggressive treatment strategies are preferred. The first-line treatment includes mainly psoralens in association with UV-A irradiation (PUVA), UV-B irradiation (or narrow-band UV-B—311 nm), interferon-α, retinoids, or a combination of these 3 modalities.[36] In many cases, patients with localized patches of the disease can also be managed with local corticosteroid ointments. Several other treatment modalities may be used as alternatives, in-

cluding topical application of chemotherapeutic agents (mechlorethamine/nitrogen mustard). By limited disease burden, in early phases, a watchful waiting strategy is also an acceptable choice.

The administration of total-body irradiation, proposed by some authors as a first-line treatment, should probably be restricted to patients with MF in advanced stages. Treatment of FMF or SMF may be more complicated because skin-directed therapies may fail to reach a depth sufficient to achieve good therapeutic results.[40] In these patients, PUVA is usually combined with retinoids. Local radiation therapy is a good option for solitary lesions of FMF or SMF.

Many different treatment modalities have been proposed over the years for the advanced stages of the diseases. A recent study showed that there is remarkable heterogeneity in treatment of advanced MF between centers in the United States and those in other parts of the world, particularly Europe.[34] Very good results with potential for cure have been obtained in several patients with allogeneic stem cell transplantation. Although toxicity is still very high, this option is promising for advanced-stage disease, particularly if patients are not heavily pretreated. Conventional systemic chemotherapy and single-agent chemotherapy (eg, gemcitabine) give usually good results in advanced MF, but recurrences are the rule. Monoclonal antibodies directed against CD52 (Alemtuzumab), CD30 (brentuximab vedotin), and chemokine receptor 4 (CCR4; mogamulizumab) have shown promising results and represent a valid alternative.[35] Extracorporeal photopheresis and total skin electron beam irradiation have been applied in advanced MF. Radiotherapy of large tumors is also a good palliative modality to improve quality of life. Nonetheless, MF remains an incurable disease in the vast majority of patients, and the need for better and more efficacious treatment modalities remains.

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