Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and accounts for approximately 50% of all primary cutaneous lymphomas. Patients with classical MF present with patches and plaques that are preferentially located on the buttocks and other covered sites of the trunk and limbs (sun-protected areas). Histopathologically, these early stages are characterized by superficial band-like or lichenoid infiltrates of small to medium-sized atypical epidermotropic T cells. Apart from this classic type of MF, many clinical and/or histopathologic variants have been described. Correct diagnosis of these MF variants is important, but may be difficult, because they may mimic a wide variety of inflammatory skin diseases. In this review, clinical and histopathologic characteristics of distinct variants of MF are presented, and their differential diagnosis and therapeutic options are discussed.

**Clinical features**

FMF is a distinct variant of MF characterized by the presence of folliculotropic infiltration, often with sparing of the interfollicular epidermis and preferential involvement of the head and neck region. In large series, FMF accounts for approximately 10% of all patients with MF. Most cases show mucinous degeneration of the hair follicles (follicular mucinosis) and were originally designated as MF-associated follicular mucinosis. Similar cases, but without follicular mucinosis, have been reported as pilotrophic MF.

It should be emphasized that FMF is defined by a combination of clinical and histopathologic criteria. Infiltration of hair follicle epithelium by neoplastic T cells can also be observed in other types of CTCL, such as CD8-positive aggressive epidermotropic cytotoxic CTCL (CD8+ AECTCL), lymphomatoid papulosis (LyP), and cases of classic MF, and is in itself insufficient for a diagnosis of FMF.

**Histopathology and immunophenotype**

Histopathologically, FMF is characterized by the presence of perifollicular to diffuse infiltrates with variable infiltration of the follicular epithelium by small, medium-sized, or sometimes large T cells with cerebriform and hyperchromatic nuclei. Many cases show mucinous degeneration of the follicular epithelium...
Mycosis fungoides variants—clinicopathologic features, differential diagnosis, and treatment

Myelium (follicular mucinosis), which can be visualized by Alcian blue or colloidal iron staining, but cases without follicular mucinosis have been described as well. Infiltration of the follicular epithelium may be accompanied by infiltration of the eccrine sweat glands (syringotropism), a combination that is often referred to as adnexotropic MF. However, concurrent infiltration of the interfollicular epidermis (epidermotropism) characteristic of early-stage classic MF is uncommon. In early-stage lesions, clinically characterized by follicle-based patches or acneiform or keratosis pililaris-like lesions, the perifollicular infiltrates are generally sparse and contain, apart from atypical T cells, variable numbers of small reactive T cells, histiocytes, and occasionally eosinophils. With progression of the skin lesions to more infiltrated plaques or tumors, the dermal infiltrates become more diffuse and may contain increasing numbers of blast cells. There is often a considerable admixture with eosinophils and, in particular, in cases with secondary bacterial infection, plasma cells. In some cases, clusters of small B cells may be present. In cases with destruction of the hair follicle epithelium, a granulomatous reaction can be observed. In cases with diffuse dermal infiltrates with partial or even complete destruction of the epithelial structures, differentiation between FMF and other types of CTCL may be challenging. Because the perifollicular infiltrates often contain scattered or clusters of CD30-positive blast cells, histopathologic differentiation between FMF and primary cutaneous CD30-positive lymphoproliferations (cutaneous anaplastic large-cell lymphoma; L3P) may be challenging. In case hair follicles have been destroyed or are completely obscured by diffuse dermal infiltrates, it may be difficult or even impossible to differentiate between FMF and primary cutaneous peripheral T-cell lymphoma, unspecified. In such cases, addi-
tional biopsies and clinical follow-up are needed to make a definite diagnosis. The relationship between FMF and the so-called benign or idiopathic form of follicular mucinosis (alopecia mucinosa) is still a matter of debate, similar to the relationship between classic MF and “parapsoriasis.” This idiopathic form of follicular mucinosis usually presents with one or a few localized patches with follicular accentuation and alopecia, particularly in children or adolescents, and has an excellent prognosis. In the case of widespread or persistent lesions, a diagnosis of FMF is more likely.

Treatment and prognosis

Previous studies emphasized that FMF is generally less responsive to several skin-directed therapies (SDTs) and runs a more aggressive clinical course similar to that of tumor-stage classic MF and should therefore be treated accordingly. However, more recent studies defined a subgroup of FMF patients with an indolent clinical behavior and an excellent prognosis, with a 5- and 10-year survival similar to that of early-stage classic MF (Table). Recognition of indolent and aggressive subgroups of FMF is also important from a therapeutic point of view because it implies that early- and advanced-stage FMF require a different therapeutic approach. Recent studies suggest a stepwise, stage-adapted therapeutic approach, similar to in early- and advanced-stage classic MF. Patients with early-stage FMF may benefit very well from nonaggressive SDT, such as topical steroids, psoralen plus ultraviolet A (PUVA), or topical nitrogen mustard. In patients with advanced-stage FMF, these SDTs are less effective. For these patients, PUVA combined with local radiotherapy, PUVA combined with interferon alfa, and/or retinoids or total skin electron beam irradiation have been recommended. For rare FMF patients presenting with a solitary plaque or tumor, local radiotherapy is highly effective and is the preferred mode of treatment. Apart from stage, advanced age, large-cell transformation, and extensive secondary bacterial infection have been reported to be associated with reduced survival.

Pagetoid reticulosis

Pagetoid reticulosis is a rare variant of MF, characterized by the presence of localized patches or plaques with an intraepidermal proliferation of neoplastic T cells. The term pagetoid reticulosis should only be used for the localized type (Woringer–Kolopp type) and not for the disseminated type (Ketron–Goodman type). Nowadays, most patients with generalized disease would be classified as primary cutaneous CD8+ AECTCL, primary cutaneous γδ T-cell lymphoma, or tumor-stage MF.

Clinical features

Patients characteristically present with a solitary, slowly progressive, psoriasiform or hyperkeratotic patch or plaque, which is usually localized on an extremity, particularly hands or feet (Figure 3).

Histopathology and immunophenotype

The typical histopathologic picture consists of a hyperplastic epidermis with marked infiltration by small to medium-sized atypical pagetoid cells, arranged singly or in nests or clusters (Figure 4). The atypical cells have medium-sized or large cerebriform nuclei and abundant, vacuolated cytoplasm. The superficial dermis may have an infiltrate of mostly small lymphocytes but rarely contains neoplastic T cells. The neoplastic T cells may show either a CD3+/CD4−/CD8+ or less commonly a CD3+/CD4+/CD8− or CD3+/CD4+/CD8− phenotype. Cases with a CD8+ or CD4+/CD8− phenotype express cytotoxic proteins. CD30 is often expressed.

Differential diagnosis

Pagetoid reticulosis should be differentiated from other types of epidermotropic CTCL, such as MF, LyP, in particular type D, and...
Mycosis fungoides variants—clinicopathologic features, differential diagnosis, and treatment

CD8⁺ AECTCL. Usef ul criteria for pagetoid reticulosis include the characteristic clinical presentation and the often strictly epidermal localization of the neoplastic T cells. CD8-positive AECTCL is characterized by a proliferation of epidermotropic CD8⁺ cytotoxic T cells and an aggressive clinical behavior. Histopathologically, early patch-like lesions may show superficial infiltrates with pronounced pagetoid epidermotropism simulating pagetoid reticulosis. However, unlike pagetoid reticulosis, these patients generally have or soon develop more widespread ulcerating papules, plaques, and tumors, showing diffuse dermal infiltrates of CD8⁺ neoplastic T cells. Epidermal necrosis and ulceration, as well as invasion and destruction of adnexal structures, are commonly found. LyP type D is characterized by marked epidermotropism of CD8⁺ cytotoxic T cells simulating CD8⁺ AECTCL as well as pagetoid reticulosis histopathologically. In contrast with CD8⁺ AECTCL, CD30 is expressed by the intraepidermal T cells in virtually all cases. Unlike pagetoid reticulosis, which may also express CD30, LyP shows the characteristic clinical course of recurrent, spontaneously regressing skin lesions and is not restricted to one acral site.

### Treatment
The preferred mode of treatment is radiotherapy or surgical exci-
sion. The prognosis of pagetoid reticulosis is excellent. In contrast with classic MF, extracutaneous dissemination or disease-related deaths have never been reported.29

Granulomatous slack skin
GSS is an extremely rare variant of MF, characterized by the slow development of folds of lax skin and a granulomatous infiltrate with clonal T cells.1,32

Clinical features
Initial skin lesions in GSS are patches and plaques as in classical MF, which evolve to bulky, pendulous folds of atrophic skin in the flexural areas (axilla and groins), resembling cutis laxa (Figure 5).33,34 In approximately one-third of the reported patients, an association with other malignant lymphomas, including MF and Hodgkin lymphoma, has been reported.34 Extracutaneous dissemination is exceedingly rare, and most patients have an indolent clinical course.2,33

Histopathology
Histopathologically, GSS is characterized by dense infiltrates throughout the entire dermis of small to medium-sized clonal T cells admixed with numerous macrophages and many scattered multinucleated giant cells (Figure 6). The presence of multinucleated giant cells containing more than 10 nuclei per cell is considered a characteristic feature, but has also been observed in cases of granulomatous MF.33 Loss of elastic tissue, elastophagocytosis, and emperipolesis (engulfment of lymphocytes) by multinucleated cells are commonly observed. The epidermis may be infiltrated by small atypical T cells with cerebriform nuclei, as in classic MF. Most cases have a CD3+/CD4+/CD8- T-cell phenotype and show clonal T-cell receptor gene rearrangement.33 In one case, a t(3;9) (q12;p24) has been reported.35

Differential diagnosis
Granulomatous MF is an unusual histopathologic variant that may be found in microscopic sections of patients with otherwise classical MF, as well as in other variants, such as FMF.36 Granulomatous changes that develop in patients with well-established MF do not usually form a diagnostic problem. However, the diagnosis may be difficult if granulomatous MF is the first manifestation of the disease, in particular in case the neoplastic T-cell infiltrate is obscured by an extensive granulomatous reaction.37 In a recent EORTC study, it was found that granulomatous MF shares many histopathologic features with GSS, including the presence of a granulomatous infiltrate with variable numbers of multinucleated giant cells, loss of elastic fibers, and a population of small to medium-sized mainly CD4+ neoplastic T cells.33 Because of these overlapping histopathologic features, histopathologic differentiation between GSS and granulomatous MF is often not possible, and the final diagnosis is ultimately based on the typical clinical presentation of GSS. Patients with granulomatous MF are reported to have a poorer response to SDTs, a worse prognosis than patients with classic MF, and a higher risk of developing a second malignant lymphoma.33,36

Treatment
Treatment of GSS is unsatisfactory. Patients have been treated with PUVA, radiotherapy, surgical excision, interferon, and other systemic therapies, but complete responses have never been reported. GSS is characterized by an indolent and slowly progressive clinical course. Because of the increased risk of a second malignant lymphoma, long-term follow-up is needed.33,38

Hypopigmented MF
Hypopigmented MF is found often in dark-skinned individuals and is the most common variant in children and adolescents.15,16,39 In white patients, hypopigmented lesions usually coexist with erythematous lesions typical of classic MF. Patients present with asymptomatic hypopigmented patches that are mainly located on trunk and extremities. Histopathology shows the typical features of early patch-stage MF. However, in contrast with classic MF, hypopigmented MF usually has a CD8+ T-cell phenotype.15,39 Patients respond very well to SDTs, preferably narrow-band UVB, and usually have an excellent prognosis.16
Other variants of MF
Apart from the variants discussed in more detail above, several other clinical and/or histopathological variants of MF have been described. Variants like hyperpigmented, bullous/vesicular, poikiloderma, pigmented purpura-like, pustular, ichthyosiform, palmoplantar MF, and still others are named after their specific clinical manifestations. However, they generally have the same typical histopathological features, and in most instances the same clinical course, as classic MF and have therefore not been included as separate entities in recent classifications for cutaneous lymphomas.

Immunophenotypical variants of MF
In addition to clinical and/or histopathological variants, phenotypical variants of MF can be distinguished also. Early-stage classic MF characteristically shows a CD3+, CD4+, CD8−, CD45RO+ T-cell helper memory cell phenotype or, even more uncommon, a CD4−, CD8+ cytotoxic T-cell phenotype, but a minority of cases may show a CD4+, CD8−, CD45RO+ T-helper memory cell phenotype, or even more uncommon, a CD4−, CD8+ or CD4+, CD8− T-cell phenotype. A CD8+ phenotype is more common in pediatric MF and in some variants of MF, including pagetoid reticulosis, hypopigmented, hyperpigmented, and poikilodermatous MF. Moreover, in rare cases of otherwise classic early-stage MF, the neoplastic T cells may express CD30 or CD56 or may have a γ/δ T-cell phenotype rather than the normal α/β T-cell phenotype. However, these aberrant phenotypes in early-stage MF do not have independent prognostic significance.

Conclusion
MF and its variants demonstrate a broad spectrum of clinical and histopathologic manifestations. By mimicking a wide variety of inflammatory dermatoses, the diagnosis of MF and in particular its variants may be challenging. Clinopathologic correlation and integration of immunophenotypical and genetic data is essential for correct diagnosis and adequate treatment.

References
24. Cerami L, Fink-Puches R, Bück B, Keel H. Follicular mucinosis: a critical reappraisal of clinicopathological features and association with mycosis fungoides and...


