

Mycosis Fungoides and Variants

Jennifer Madison McNiff, M.D.
Associate Professor, Dermatology and Pathology
Yale University School of Medicine

Classic mycosis fungoides

The most common cutaneous lymphoma is known historically as mycosis fungoides (MF), and represents about 50-60% of all cutaneous lymphomas. The broader term “cutaneous T-cell lymphoma” has also been applied to mycosis fungoides and related conditions such as Sezary syndrome, but it is important to recognize that there are several forms of T-cell lymphoma in the skin unrelated to mycosis fungoides, including CD30-positive large cell anaplastic lymphoma, subcutaneous panniculitic lymphoma, pleomorphic T-cell lymphoma, and other miscellaneous peripheral T-cell lymphomas.

Clinically, MF typically presents as annular patches and plaques affecting sun-protected sites such as buttocks or axillae. Older adults are most commonly affected, but MF does occur in children as well. Disease progression is slow, with tumors developing in some patients as a late event. Transformation to large cell lymphoma is associated with a poor prognosis.

Histologically, the changes of MF are often subtle, requiring multiple biopsies over extended periods of time to secure a diagnosis. Various patterns of epidermotropism are useful criteria in the diagnosis of MF. “Disproportionate epidermotropism,” refers to significant numbers of intraepidermal lymphocytes disproportionate to the degree of spongiosis in the biopsy, and is a helpful if not highly sensitive or specific criterion. Pautrier’s microabscesses have been variably defined as clusters of few to several atypical lymphocytes in the epidermis, often in association with Langerhans cells. These cellular aggregates are nearly pathognomonic of MF, although they are typically seen in only a minority of early biopsies (with an incidence ranging for 3 to 30% depending on the study).

An important pattern of epidermotropism in MF is “linear basilar epidermotropism.” For reasons unknown, the malignant lymphocytes in MF tend to line up along the basal layer of the epidermis like a “row of toy soldiers” or a “string of pearls.” This pattern is considered a highly sensitive, albeit less specific, feature of early MF.

Another helpful histologic criterion is that of “haloed lymphocytes,” a term that reflects the tendency of malignant intraepidermal lymphocytes to show artifactual cytoplasmic retraction, giving the impression of haloes around the nuclei. This feature has been reported in about 60% of MF, and 13 % of inflammatory dermatoses, representing a fairly robust diagnostic criterion.

The finding of intraepidermal lymphocytes larger than dermal lymphocytes also strengthens the histologic diagnosis of MF. This feature reflects the fact that early in disease, a clonal malignant lymphocyte population is present in the epidermis, while the dermal infiltrate typically is comprised of reactive CD8 positive cytotoxic lymphocytes.

Finally, in a recent review by Santucci and colleagues, the finding of medium large cerebriform lymphocytes in the epidermis is reported to offer a high degree of sensitivity and specificity in the diagnosis of MF. These cells are defined as lymphocytes with a nuclear diameter the same size or larger than neighboring keratinocytes (7-9 microns). Other studies question the helpfulness of this finding, either because such cells are infrequently present in MF, or because of the inherent interobserver variability in judging lymphocyte atypia.

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Smoller BR et al. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. *Am J Surg Pathol* 19:1423, 1995.

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Glusac EJ, Shapiro PE, McNiff JM. Cutaneous T-cell lymphoma. Refinement in the application of controversial histologic criteria. *Dermatol Clin* 17:601, 1999.

Glusac EJ. Of cells and architecture. *J Cutan Pathol* 28:169, 2001

Diagnostic pitfalls

Because so many inflammatory dermatoses mimic MF not only histologically but clinically as well, it has been suggested that the best way to rule out MF may be to make another diagnosis. Some of the common pitfalls are discussed briefly below.

Spongiotic dermatitis vs mycosis fungoides

Spongiotic dermatitis is one of the most common considerations in the clinical and histologic differential diagnosis of MF. Some forms of dermatitis in particular, such as allergic contact dermatitis, are notable for their close histologic similarity to MF (for which the term "lymphomatoid contact dermatitis" has been coined).

Histologically, the finding of nonlymphoid intraepidermal mononuclear cell collections (pseudopautrier microabscesses) favors the possibility of spongiotic dermatitis. These collections are distinguished by their flask shape in the epidermis, and by the presence of Langerhans cells and precursors (staining CD1a+, S100+, CD68+, CD83+). However, since approximately 10% of cases of MF also feature spongiosis, the presence of

pseudopautrier microabscesses alone does not confirm a benign diagnosis. In fact, in a study by Candiago, while pseudopautrier microabscesses were found in 43% of cases of spongiotic dermatitis, they were also observed in 13% of cases of MF. Subtle clues favoring the diagnosis of MF over spongiotic dermatitis in difficult cases include a spongiotic-psoriasiform-lichenoid pattern, the presence of purpura, epidermal atrophy and hyperplasia in a single silhouette, and a uniform laminated horn.

References:

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Candiago E et al. Nonlymphoid intraepidermal mononuclear cell collections (pseudopautrier abscesses). A morphologic and immunophenotypical characterization. *Am J Dermatopathol* 22:1-6, 2000.

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Orbaneja JG et al. Lymphomatoid contact dermatitis: a syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides. *Contact Dermatitis* 2, 139-143, 1976.

Drug-induced pseudolymphoma vs mycosis fungoides

There is ample attention in the literature to the problem of drug reactions mimicking MF. Drug induced pseudolymphoma, in particular due to Dilantin, exemplifies this phenomenon. In general, patients with this condition have a fever, generalized rash, and lymphadenopathy. However, there are also reports of cutaneous lesions resembling MF secondary to medications without systemic symptoms. Clearly, clinical history is essential in this differential diagnosis. Histologically, it can be difficult if not impossible to differentiate between drug induced pseudolymphoma and true MF. In addition, some drug-induced pseudolymphomas show clonal gene rearrangements, making a distinction by molecular methods suspect. Usually drug induced pseudolymphoma resolves with cessation of drug therapy and recurs with rechallenge.

Drugs mimicking MF

CLINICAL MIMICS

phenytoin
carbamazepine
fluoxetine

HISTOLOGIC MIMICS

phenytoin, carbamazepine
fluoxetine
enalopril, captopril
quinine
atenolol
phenobarbital
d-penicillamine
antihistaminic drugs

References:

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Lichenoid dermatitis (LP, LSA, PPE) vs mycosis fungoides

The histologic distinction between some lichenoid dermatoses and lichenoid presentations MF can at times be problematic. In a review of the distinction between early lichen sclerosus (LS) and lichen planus (LP), LeBoit et al noted that 100% of cases of early LSA show a psoriasiform lichenoid pattern (also common in MF), 100% showed basilar epidermotropism (as in MF), and 33% showed epidermal atrophy, also common in MF. While in that study, such features helped distinguish cases of LS from LP, the results underscore the potential similarities between LS and MF. Decreased elastic fibers and a thickened basement membrane favor LS, and are not typical in MF. Clearly, the clinical features should be helpful diagnostically as well.

Some cases of lichenoid MF closely resemble lichen planus (LP) histologically. Guitart et al published a series of cases of MF with lichenoid features bearing a close histologic resemblance to LP, but also showing plasma cells, eosinophils, lymphocyte atypia and prominent basilar epidermotropism. Clinically, the cases were notable for intense pruritis and an accelerated course, suggesting that lichenoid MF may have a worse prognosis than other presentations of MF.

Examples of lichenoid pigmented purpura may share many histologic features with MF, and there is current debate whether cases of persistent pigmented purpuric dermatitis (PPPD) represent a simulant of MF, a precursor, or both. In a recent review of 56 patients with PPPD by Toro et al, 29 cases showed histologic patterns typical of MF. Further, clonal gene rearrangements were found in 8 of 12 specimens showing a lichenoid pattern of PPPD that resembled MF. There are also reports of PPPD preceding or occurring concurrently with MF, further suggesting a relationship between these processes. Interestingly, the first patient reported in the American literature as having lichen aureus later proved to have MF. Both PPPD and MF may show lymphocytes in the lower epidermis, linear epidermotropism, and papillary dermal fibrosis. Features favoring the diagnosis of MF include large collections of lymphocytes in the epidermis with many lymphocytes in the spinous layer, and lymphocyte atypia. The presence of edema of the papillary dermis favors the diagnosis of PPPD.

Another common entity which may closely mimic MF histologically is the benign lichenoid keratosis (BLK) or lichen planus-like keratosis (LPLK). Such cases have aptly been termed mycosis fungoides-like keratosis (MFLK) or lymphomatoid lichenoid keratosis (LLK). In general, clinical findings such as size and duration, and histologic findings such as epidermal destruction should enable a distinction between MFLK and true solitary lesions of MF (see chart below).

MFLK (LLK, BLK, LPLK)

trunk and extremities
small and scaly (< 1 cm)
short duration
clinical usually R/O CA
bx MF-like, epidermal destruction
polyclonal

Unilesional MF

often acral
usually > 1 cm
usually longer duration
clinical rash, dermatitis, MF
bx MF
monoclonal

References:

Cerroni L et al. Solitary skin lesions with histopathologic features of early mycosis fungoides. *Am J Dermatopathol* 21:518-524, 1999.

Citarella L et al. Lichen sclerosus with histopathologic features simulating early mycosis fungoides. *Am J Dermatopathol* 25:463-465, 2003.

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Toro JR et al. Persistent pigmented purpuric dermatitis and mycosis fungoides: simulant, precursor, or both? A study by light microscopy and molecular methods. *Am J Dermatopathol* 19:108-118, 1997.

Variants of MF

Further confounding our ability to make a definitive diagnosis of MF is the presence of many unusual clinical and histologic variants of this disease. The more common of these will be discussed below.

Woringer Kolopp disease (pagetoid reticulosis)

In 1939, Woringer and Kolopp described a solitary cutaneous plaque on the foot of a 13-year old child, characterized by intraepidermal lymphocytes. Since then, the term

Woringer-Kolopp disease has been applied to solitary lesions of the skin with a histologic pattern typical of mycosis fungoides, featuring prominent lymphocytic epidermotropism, often with minimal dermal infiltrates. The lymphocytes tend to reside in the epidermis with small haloes, hence the resemblance to Paget's disease for which the term "pagetoid reticulosis" was coined. Cases typically show an indolent clinical course. In the past, there has been considerable debate in the literature about the relationship between Woringer-Kolopp disease and mycosis fungoides. Despite the histologic similarity between Woringer-Kolopp and classic MF, the lymphocytes of Woringer-Kolopp disease are as likely to show a T-suppressor phenotype (CD8 positive) as they are to be CD4 positive, and gene rearrangements have not been consistently identified in examined cases.

Nonetheless, reports are accumulating in the literature of solitary lesions of mycosis fungoides, analogous to Woringer-Kolopp disease, some of which do show gene rearrangements, and a few of which show progression to widespread MF. Clinically, lesions historically classified as Woringer-Kolopp disease favor acral sites; the term "mycosis fungoides palmaris et plantaris" has been applied to such lesions. In a recent report describing 20 lesions of solitary MF, Cerroni emphasized involvement of the trunk and extremities. All cases showed a band-like dermal infiltrate with epidermotropism, and moderate lymphocyte atypia. T cell receptor gene rearrangements were detected in half the cases tested. The authors concluded that cases of solitary MF exist, show a relatively indolent course, and can be treated conservatively, but should be followed for potential progression to more widespread disease.

References:

McNiff JM et al. Mycosis fungoides palmaris et plantaris or acral pagetoid reticulosis? *Am J Dermatopathol* 20:271-275, 1998.

Cerroni L et al. Solitary skin lesions with histopathologic features of early mycosis fungoides. *Am J Dermatopathol* 21:518-524, 1999.

Granulomatous slack skin

Granulomatous slack skin is a rare and clinically dramatic disease, featuring large pendulous folds of skin typically in the axillae and groin, with erythema and scale. There is a female predominance. Histologically, there are sheets of granulomas and lymphocytes in the dermis. Numerous giant cells are present, and are notable for containing 30 to 40 nuclei per cell. Elastic tissue stains demonstrate complete loss of elastic fibers throughout the dermis. Fragments of elastic fibers as well as lymphocytes are identified in multinucleated giant cells. The superficial dermis may contain features more typical of MF, including papillary dermal fibrosis, a band-like lymphocytic infiltrate, and epidermotropism. Molecular studies have revealed T cell clonality, further supporting the diagnosis of lymphoma. Cases tend to be indolent or slowly progressive. It should be noted that otherwise typical cases of MF sometimes also show granulomatous inflammation, the etiology of which is unclear. This change seems

unrelated to clinical parameters in any given case, and is not associated with the dramatic pendulous skin folds of granulomatous slack skin.

References:

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Metzler G et al. Granulomatous mycosis fungoides. Report of a case with some histopathologic features of granulomatous slack skin. *Am J Dermatopathol* 21:156-160, 1999.

Adnexotropic mycosis fungoides (folliculotropic and syringotropic patterns)

A relationship between follicular mucinosis and MF is well documented, occurring primarily in the head and neck as pruritic plaques with concurrent alopecia, and lymphocytes invading follicles distorted by mucin deposition. Follicular involvement in MF may also occur as keratotic plaques and cysts comprised histologically of dense aggregates of lymphocytes invading follicular epithelium, without mucin in follicles or changes of MF in the overlying epidermis. Recognition of folliculotropic MF is important, whether or not there is accompanying follicular mucinosis, since folliculotropic lesions tend to be recalcitrant to superficial therapy such as photochemotherapy, and require alternative treatment such as with electron beam.

Cases have been reported in which lesions of MF are predominately syringotropic, again with minimal epidermal involvement. In the early 1990's, this phenomenon was reported as "syringolymphoid hyperplasia with alopecia". Clinically, this variant features plaques studded with papules. Histologically, the eccrine apparatus is hyperplastic and diffusely infiltrated with atypical lymphocytes. As with cases of folliculotropic MF, classification as lymphoma relies on the presence of cytologic atypia, T-cell gene rearrangements, and usually the presence of more classic lesions of MF elsewhere in the same patient. It is interesting to note that in classic lesions of MF, involvement of eccrine glands is visible in approximately one third of cases, and involvement of follicles can be seen in about half of cases, further demonstrating the tendency for adnexotropism of the malignant lymphocytes in this disease.

References:

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James et al. Syringolymphoid hyperplasia with alopecia. *J Cutan Pathol* 21:520-526, 1994.

Hitchcock MG et al. Eccrine gland infiltration by mycosis fungoides. *Am J Dermatopathol* 18:447-453, 1996.

Hypopigmented mycosis fungoides

Another rare variant of mycosis fungoides presents with hypopigmentation. Although this variant is more common in dark-skinned patients, it can be seen in Caucasians as well. Younger patients seem more often affected by this disorder, with a median age of 15 years, and a female predominance in cases reported to date. Typically, clonality of epidermotropic T-cells can be detected. The malignant clone is often composed of CD8+ rather than CD4+ lymphocytes. Persistent or unusual hypopigmented lesions, particularly in younger age groups, should be biopsied to assess the possibility of mycosis fungoides and enable prompt treatment.

Ardigo J et al. Hypopigmented mycosis fungoides in Caucasian patients: a clinicopathologic study of 7 cases. *J Am Acad Dermatol* 49:264-70, 2003.

Shabrawi-Caelen LE, et al. Hypopigmented mycosis fungoides. Frequent expression of a CD8+ T-cell phenotype. *Am J Surg Pathol* 26:450-457, 2002.

Sezary Syndrome

The triad of erythroderma, generalized lymphadenopathy, and neoplastic T lymphocytes (Sezary cells) in the skin and blood defines Sezary syndrome. Importantly for the histopathologist, the cutaneous infiltrates of Sezary syndrome may not show specific features of MF, and diagnosis must be established by immunophenotypic and genotypic studies of the circulating lymphocytes in these patients. The prognosis is generally poor, and patients are at risk of opportunistic infection due to immunosuppression.

Willemze R et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 105:3768-3785, 2005.