INTRODUCTION

Just as mycosis fungoides is a disease with many different clinical and histologic manifestations, so too are there many inflammatory conditions that mimic this cutaneous lymphoma. Sometimes the best way to “rule out” a diagnosis of mycosis fungoides is to make a firm diagnosis of another condition. The following entities may be confused with mycosis fungoides on histologic grounds, and represent potential diagnostic traps for the unsuspecting pathologist. Awareness of the spectrum of histologic findings described below will help prevent over-diagnosis and over-treatment of patients.

LECTURE OBJECTIVES

1. To identify the most common rashes that mimic mycosis fungoides
2. To recognize histologic variants of mycosis fungoides that are commonly mistaken as mimics of disease
3. To appreciate the complexity in distinguishing benign from malignant cutaneous lymphoid infiltrates, and the importance of clinicopathologic correlation in doing so.

Spongiotic dermatitis vs mycosis fungoides

Mycosis fungoides (MF) is a disease with a wide variety of clinical and histologic presentations. For this reason, there is a broad spectrum of diseases, which mimic MF, particularly at the light microscopic level. Spongiotic dermatitis is perhaps best known for its potential to mimic MF, particularly because 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). Among the examples in the literature are cases of reaction to chewing gum wrapper in a trouser pocket, reaction to rubber eraser in a pocket, and reaction to the striker area of a matchbox in a hip pocket, all simulating plaques of MF both clinically and histologically.

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:


4. 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 MF**

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 in which other features of this syndrome are not present. 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. The list of drugs reported to mimic MF is ever growing (see below). For all these reasons, some investigators recommend withdrawal of all noncritical medications prior to making an initial diagnosis of MF, and prior to initiating therapy. Usually drug induced pseudolymphoma resolves with cessation of drug therapy and recurs with rechallenge. However, there are also occasional reports of true lymphoma developing after drug-induced pseudolymphoma, despite discontinuation of medications. In a report by Li et al, malignant lymphoma (of all types, not just MF) was seen 2-10 times more frequently in patients treated with Dilantin than in a control population.

**Drugs mimicking MF**

<table>
<thead>
<tr>
<th>CLINICAL MIMICS</th>
<th>HISTOLOGIC MIMICS</th>
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<tbody>
<tr>
<td>phenytoin</td>
<td>phenytoin, carbemazepine</td>
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<tr>
<td>carbemazepine</td>
<td>fluoxetine</td>
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<td>fluoxetine</td>
<td>enalopril, captopril</td>
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<td>atenolol</td>
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<td>phenobarbital</td>
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<td></td>
<td>d-penicillamine</td>
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<td>antihistaminic drugs</td>
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**References:**


**Lichenoid dermatitis vs MF**

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. However, the potential for error resulting from incomplete clinical correlation was apparent in our institution recently when a patient with early vulvar LSA was referred to the lymphoma clinic carrying the histologic diagnosis of MF.

Some cases of lichenoid MF closely resemble LP histologically. In an comprehensive review of the histology of MF by Shapiro et al, features favoring a diagnosis of lichenoid MF over LP include a deep infiltrate, laminated horn or parakeratosis, lack of hypergranulosis, and minimal vacuolar change. 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 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, which 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. A recent review of lichen aureus showed monoclonal gene rearrangements in about half of the cases, but there was no evidence of progression to MF in this series of 23 patients.

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).

<table>
<thead>
<tr>
<th>MFLK (LLK, BLK, LPLK)</th>
<th>Unilesional MF</th>
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<tbody>
<tr>
<td>trunk and extremities</td>
<td>often acral</td>
</tr>
<tr>
<td>small and scaly (&lt; 1 cm)</td>
<td>usually &gt; 1 cm</td>
</tr>
<tr>
<td>short duration</td>
<td>usually longer duration</td>
</tr>
<tr>
<td>clinical usually R/O CA</td>
<td>clinical rash, dermatitis, MF</td>
</tr>
<tr>
<td>bx MF-like, epidermal destruction</td>
<td>bx MF</td>
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<tr>
<td>polyclonal</td>
<td>monoclonal</td>
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References:


**Superficial and deep infiltrates mimicking MF**

Dermatoses showing superficial and deep inflammation may also mimic MF. In the literature, there are reports of DLE, lichen striatus, and pityriasis lichenoides all simulating MF. Clinically, DLE and lichen striatus are usually readily recognizable. Histologically, the persistent presence of exocytosis and of appendageal involvement in 92% cases of *lichen striatus* reported by McNutt bears mentioning because of potential confusion with adnexotropic variants of MF.

In contrast, the distinction, and possible overlap, between some cases of MF and pityriasis lichenoides (PL) remains a challenge for the pathologist and clinician alike. Histologically, the presence of marked exocytosis in PL can mimic epidermotropism of MF. The presence of obvious interface change enables classification as PL, yet some cases of MF also show interface change, confounding this distinction. While parakeratosis is not uncommon in MF, it is rare to see parakeratosis and neutrophils together in cases of MF as is typical of PL.

Although PL has long been regarded as a benign inflammatory dermatosis, recent studies showing clonal gene rearrangements in PLEVA and PLC have led to the proposal that PL be reclassified as a T cell lymphoproliferative process (Wiess, Fortson). Supporting the concept of a connection between these disorders are rare reports of children with documented PLEVA evolving into MF. Further confounding the distinction between PL and MF are reports of children with clinical features of PLEVA, who show diagnostic histologic features of MF. Using light microscopic criteria, most cases of PL and MF can successfully be classified. However, the significance of clonal gene rearrangements in PL, and the overlap in some patients between PL and MF, remains to be clarified.

**References:**


**MF-like infiltrates in patients with HIV infection**

Although there are reports of lymphoma arising in patients with HIV disease, these are usually high-grade extranodal B cell lymphomas. There are some reports of rashes in HIV positive patients that clinically and histologically resemble MF, some of which have been reported as MF. In cases studied immunophenotypically, however, the infiltrating T cells show a predominance of CD8 positive cells. Molecular studies to date have not shown clonality of infiltrating lymphocytes. In some cases, these rashes are associated with profound lymphopenia and advanced HIV infection, and are associated with a poor outcome. Although there are many clinical and histologic resemblances to MF in these patients, when such lesions are confined to skin, composed of predominately CD8 positive cells, and lack
clonality, pathologists should be cautious about the possibility that these lymphoid infiltrates represent a mimic of MF. Further complicating interpretation of these rashes are reports of patients co-infected with HIV and HTLV-I or HTLV-II. In the latter cases, patients have been reported to develop erythroderma and desquamation, with clonal CD8 positive cutaneous lymphoid infiltrates resembling MF. The biologic significance of such rashes is difficult to assess, because patients often have a greatly shortened lifespan due to advanced immunodeficiency, precluding follow-up of the evolution of the cutaneous lesions.


**Conclusion**

Perhaps as our understanding of MF progresses and histologic criteria are further refined, and with the advent of sophisticated molecular testing, these differential diagnoses will prove less problematic. However, the gold standard in the distinction between MF and its mimics remains strong clinical correlation, and careful consideration of all histologic criteria for MF.