Actas Dermosifiliogr. 2017;xxx(xx):xxx–xxx

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

REVIEW

Clinicopathologic Variants of Mycosis Fungoides☆

H. Muñoz-González, A.M. Molina-Ruiz,* L. Requena

Servicio de Dermatología, Hospital Universitario Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid, Spain

Received 17 May 2016; accepted 4 August 2016

KEYWORDS
Cutaneous lymphomas;
Mycosis fungoides;
Variants;
Dermatopathology

Abstract Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma. The clinical course of the disease is typically characterized by progression from a nonspecific phase of erythematous macules to the appearance of plaques and ultimately, in some patients, tumors. However, numerous clinical and histopathologic variants of MF with specific therapeutic and prognostic implications have been described in recent decades. Clarification of the differential diagnosis can be frustrated by the wide range of clinical manifestations and histopathologic patterns of cutaneous infiltration, particularly in the early phases of the disease. In this paper, we review the main clinical, histopathologic, and immunohistochemical characteristics of the variants of MF described in the literature in order to facilitate early diagnosis of the disease.

PALABRAS CLAVE
Linfomas cutáneos;
Micosis fungoide;
Variantes;
Dermatopatología

Variantes clínico-patológicas de micosis fungoide

Resumen La micosis fungoide (MF) es el linfoma primario cutáneo de células T más frecuente. La evolución clínica clásica de la enfermedad se caracteriza por la progresión desde una fase inespecífica de máculas eritematosas a la aparición de placas y, finalmente, tumores en algunos pacientes. Sin embargo, a lo largo de las últimas décadas se han descrito numerosas variantes de MF, tanto desde el punto de vista clínico como histopatológico, con implicaciones terapéuticas y pronósticas específicas. El diagnóstico diferencial se ve dificultado así ante el amplio abanico de manifestaciones clínicas y patrones histopatológicos de infiltración cutánea, especialmente en fases precoces de la enfermedad. Este artículo revisa las principales características clínicas, histopatológicas e inmunohistoquímicas que definen las distintas variantes de MF descritas en la literatura con el objetivo de facilitar el diagnóstico temprano de MF.

☆ Please cite this article as: Muñoz-González H, Molina-Ruiz AM, Requena L. Variantes clínico-patológicas de micosis fungoide. Actas Dermosifiliogr. 2016. http://dx.doi.org/10.1016/j.ad.2016.08.009
* Corresponding author.
E-mail address: amolinar@fjd.es (A.M. Molina-Ruiz).

Introduction

Mycosis fungoides (MF) is the most common primary T-cell cutaneous lymphoma and accounts for almost 50% of all primary cutaneous lymphomas.[1] Described for the first time in 1806 by the French dermatologist Jean Louis Alibert, classic MF starts with a nonspecific phase consisting of erythematous macules that can last for years. In subsequent phases, patients develop plaques and, in some cases, tumors. The name *mycosis fungoides* refers to the mushroom-like appearance of the tumors. Enlarged lymph nodes, visceral involvement, and transformation to large-cell lymphoma are less common findings that are typically seen in advanced stages of the disease. Numerous clinical and histopathologic variants of MF have been described in recent decades. Although some of these variants have been reported as isolated cases, others have greater clinical relevance due to their relative frequency and their therapeutic and prognostic implications. The wide range of clinical and pathological presentations of early-stage MF requires a broad differential diagnosis as early lesions can mimic many of the patterns seen in cutaneous inflammatory disorders.

In this article, we review the main clinical, histopathologic, and immunohistochemical characteristics that help to establish a correct diagnosis of MF, particularly in the early stages of disease. We also describe the distinctive clinical and pathological features that define the different variants of MF.

Classic MF

MF has traditionally been defined as a 3-stage disorder characterized by the progressive appearance of patches, plaques, and tumors. Not all patients, however, pass through these 3 stages. Some remain in the plaque stage, showing no signs of disease progression, while others develop patches, plaques, and tumors as a presenting form of the disease.

Patch-Stage MF

Patch-stage MF is clinically characterized by the presence of asymmetric, irregular, erythematous macules and patches occasionally associated with atrophy and/or telangiectasia.[2] The lesions are generally asymptomatic or mildly pruritic and disappear spontaneously, without leaving residual lesions (Fig. 1A). Patch-stage MF can last for years, with no signs of progression. It is not associated with worse outcomes than other forms of MF and patients have a similar life expectancy to the general population.[3]

The histopathologic features of patch-stage MF include scarce lymphocytes scattered through the basal layers of the epidermis, accompanied by focal parakeratosis, papillary dermal fibrosis, and a larger population of lymphocytes arranged in a band-like pattern along the dermal-epidermal junction. Additional findings include a predominantly lymphocytic perivascular, periadnexal, or subepidermal infiltrate with eosinophils and some plasma cells (Fig. 1B and C). Intraepidermal lymphocytes are generally larger and more pleomorphic than lymphocytes found in the superficial dermis, and on occasions they are surrounded by a pale cytoplasmic halo. These morphologic features are highly indicative of MF, but they are not consistent, and repeat skin biopsies over time are often necessary to establish a definitive diagnosis of patch-stage MF.[4]

Plaque-Stage MF

Plaque-stage MF is characterized by well-demarcated erythematous or dark brown plaques that are often pruritic and accompanied by scaling. They generally affect a large area of skin (Fig. 1D). Plaques and characteristic macules from earlier stages frequently coexist in the same or different areas.[5,6]

Plaque-stage MF has similar histopathologic features to patch-stage MF but it has a denser band-like lichenoid lymphocytic infiltrate in the superficial dermis. This infiltrate is primarily composed of small and medium-sized lymphocytes with pleomorphic hyperchromatic nuclei and numerous convolutions that lend it a cerebriform appearance (Fig. 1E and F). Epidermotropism is frequently more pronounced in plaque-stage than in patch-stage MF and is characterized by the presence of atypical lymphocytes in the epidermis that occur in isolation or form collections known as *Pautrier microabscesses*. Other common findings include epidermal hyperplasia, papillary dermal fibrosis, and some eosinophils and plasma cells in the accompanying inflammatory infiltrate.

Tumor-Stage MF

Skin tumors are the key clinical feature of tumor-stage MF and they frequently coexist with patches and plaques (Fig. 1G). The absence of patches and plaques should lead to a reassessment of diagnosis and the inclusion of other more aggressive non-MF cutaneous lymphomas in the differential diagnosis. MF tumors are characterized by significant vertical growth, giving rise to smooth reddish-brown or bluish-red nodules that can reach a size of several centimeters and become ulcerated or infected.[7]

Histopathologic findings include a diffuse nodular lymphocytic infiltrate formed by large pleomorphic lymphocytes with hyperchromatic nuclei and prominent nucleoli occupying the full thickness of the dermis and possibly extending into the subcutaneous tissue (Fig. 1H and I). The cells in the infiltrate frequently have a high proliferative index and typical and atypical mitotic figures are abundant. Pautrier microabscesses and epidermotropism are normally absent in the tumor stage of MF.

Diagnosing MF

Pathologic diagnosis of early-stage MF is challenging not only because of the subtle nature of the histopathologic findings, but also because of overlapping with features seen in other inflammatory skin disorders. This is further complicated by the absence of certain characteristic clinical and histopathologic findings in early MF. Pautrier microabscesses, for instance, are observed in less than 25% of cases, atypical lymphocytes are found in less than 10% of cases, and