

# Mycosis fungoides

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## Abstract

*Mycosis fungoides represents the most common type of cutaneous T-cell lymphoma. Its incidence has been estimated to 0.36/10<sup>5</sup> person-years. It affects adults or the elderly. Three clinical stages can be recognized: one characterized by patches, one by patches and/or plaques, and one by patches, plaques, and/or tumours. In the early stages, preferential location is the buttocks and other sun-protected areas. Histology reveals predominance of small pleomorphic (cerebriform) cells. During disease course large cell transformation may occur indicating a worse prognosis (immunoblasts, large anaplastic cells, large pleomorphic cells). In most cases, immunohistology shows a memory T-helper phenotype (CD3+, CD4+, CD45Ro+, CD8-, 45Ra-). CD30 and cytotoxic markers (i.e., TIA-1) may be positive in late stages in tumors with large cell morphology. A monoclonal rearrangement of the TCR gene is absent in about 50% of patients in the early phases. Treatment strategies include in early phases mainly PUVA (photochemotherapy), interferon  $\alpha$ -2a, retinoids (alone or in combination), topical chemotherapy, topical steroids, narrow-band UV-B (311 nm), and photodynamic therapy. Advanced disease can be treated by systemic chemotherapy, extracorporeal photopheresis, and/or radiotherapy (including total body electron beam irradiation). New experimental treatment modalities include new retinoids (i.e., bexarotene), imiquimod, new chemotherapeutic drugs (i.e., gemcitabine, fludarabine, pegylated doxorubicine), pentostatin, and allogeneic stem cell transplantation. Aetiology has not been determined yet.*

**Keywords:** cutaneous T-cell lymphoma, patches, plaques, tumour, erythroderma, PUVA, , interferon  $\alpha$ -2a, retinoid, TCR gene

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## Definition

Mycosis fungoides represents the most common type of cutaneous T-cell lymphoma.<sup>1,2</sup>

Traditionally it is divided into three clinical phases: patch-, plaque-, and tumour-stage. The

clinical course can be protracted over years or decades.

### Excluded diseases

The term "mycosis fungoides" should be restricted to the classical so-called "Alibert-Bazin" type of the disease, characterized by the typical slow evolution and protracted course. More aggressive entities (e.g., mycosis fungoides "a tumeur d'emblee"), characterized by onset with plaques and tumours, aggressive course, and bad prognosis, are better classified among the recently described group of cutaneous cytotoxic T- (NK/T)-cell lymphomas.

### Disease course

In the past mycosis fungoides has been considered as an "incurable", albeit slowly progressive disease, that inevitably ended in death of patients. Recently, identification and definition of criteria for clinicopathologic diagnosis of small patches allowed identification of patients with early mycosis fungoides,<sup>3-5</sup> who often present with a relatively mild course and prolonged survival, without progression into plaque and tumour-stage. The inevitability of disease progression and death due to lymphoma, thus, has to be questioned.

### Frequency

Mycosis fungoides is a rare disease. According to a survey, incidence was reported to be 0.36/10<sup>5</sup> person-years from 1973 to 1992 in the United States<sup>6</sup>.

### Aetiology

The aetiology of mycosis fungoides is yet unknown. Genetic predisposition may play a role in some cases, and familial occurrence has been reported in a few instances. Association with long-term exposure to various allergens has also been advocated, as well as exposure to environmental agents and association with chronic skin disorders and viral infections. In some countries, mycosis fungoides-like disorders are clearly associated with viral infections (*i.e.*, HTLV-I-associated adult T-cell lymphoma/leukaemia), but search for viral particles in patients with mycosis fungoides has been unsuccessful.

### Associated diseases

Mycosis fungoides has been described in patients with other haematological disorders, especially lymphomatoid papulosis and Hodgkin's lymphoma. In occasional patients, the same clone has been detected in mycosis fungoides and associated lymphomas, raising questions about a common origin of the diseases.<sup>7-9</sup> In addition, patients with mycosis

fungoides are at higher risk of developing a second (non-haematological) malignancy.<sup>10</sup>

### Disease classification

A staging classification system for mycosis fungoides was proposed in 1979 by the Mycosis Fungoides Cooperative Group (TNMB - tumour-node-metastasis-blood-staging) (**Table 1**).<sup>11</sup> This system takes into account the percentage of body area covered by lesions, and the presence of lymph node or visceral involvement. Although the presence of malignant circulating cells in the blood should be recorded for each patient, these data are not used for staging.

### Clinical features

#### **Cutaneous involvement**

Lesions of mycosis fungoides can be divided morphologically into patches, plaques, and tumours. Itching is often a prominent symptom. Erythroderma may develop at some point, making it difficult to distinguish it from Sezary syndrome without proper clinical history. Patches of mycosis fungoides are characterized by variably large, erythematous, finely scaling lesions mostly located on the buttocks and other sun-protected areas. Plaques of mycosis fungoides are characterized by infiltrated, scaling, reddish-brown lesions. In tumour-stage mycosis fungoides a combination of patches, plaques and tumours is usually found, but tumours may be observed also in the absence of other lesions.

#### **Extracutaneous involvement**

Lymph nodes, lung, spleen and liver are the most frequent sites of extracutaneous involvement, but specific lesions can arise in all organs. Because of the presence of ulcerated tumours and of immune deficiency (due to both lymphoma and the many treatments typically administered to these patients), septicaemia and/or pneumonia are the major causes of death.

### **Histopathology, immunohistology and molecular biology**

It should be clearly stated that, although precise histopathologic criteria for the diagnosis of early mycosis fungoides have been identified, in many cases only correlation with the clinical features of the disease allows a precise diagnosis to be made.

**Table 1. TNMB\* staging of mycosis fungoides**<sup>2-5</sup>

**Skin**

T <sub>1</sub>	Patches, papules or plaques covering <10% of the skin surface
T <sub>2</sub>	Patches, papules or plaques covering >10% of the skin surface
T <sub>3</sub>	Tumours
T <sub>4</sub>	Generalized erythroderma

**Lymph nodes**

N <sub>0</sub>	No clinically abnormal lymph nodes; histology negative
N <sub>1</sub>	Clinically abnormal peripheral lymph nodes
N <sub>1o</sub>	Histology not performed
N <sub>1n</sub>	Histology negative
N <sub>1r</sub>	Histology reactive
N <sub>1d</sub>	Dermopathic lymphadenitis
N <sub>2</sub>	No clinically abnormal peripheral lymph nodes; histology positive
N <sub>3</sub>	Clinically abnormal peripheral lymph nodes; histology positive

**Visceral organs**

M <sub>0</sub>	No visceral involvement
M <sub>1</sub>	Visceral involvement

**Blood**

B <sub>0</sub>	<5% of atypical circulating cells
B <sub>1</sub>	>5% of atypical circulating cells

**Stages**

<b>Ia</b>	T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	<b>Ib</b>	T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>
<b>Ila</b>	T <sub>1-2</sub> N <sub>1</sub> M <sub>0</sub>	<b>Ilb</b>	T <sub>3</sub> N <sub>0-1</sub> M <sub>0</sub>
<b>III</b>	T <sub>4</sub> N <sub>0-1</sub> M <sub>0</sub>		
<b>IVa</b>	T <sub>1-4</sub> N <sub>2-3</sub> M <sub>0</sub>	<b>IVb</b>	T <sub>1-4</sub> N <sub>0-3</sub> M <sub>1</sub>

\*Tumor-node-metastasis-blood

**Histopathology**

Early lesions of mycosis fungoides reveal a patchy lichenoid or band-like infiltrate in an expanded papillary dermis. Small lymphocytes predominate and atypical cells can be observed only in a minority of the cases. Epidermotropism of solitary lymphocytes is usually observed, but so-called Pautrier's microabscesses are rare. Useful diagnostic clues are the presence of epidermotropic lymphocytes with nuclei slightly larger than those of lymphocytes within the upper dermis and/or the presence of lymphocytes aligned along the basal layer of the epidermis. The papillary dermis shows a moderate to marked fibrosis with coarse bundles of collagen.

Plaques of mycosis fungoides are characterized by a dense, band-like infiltrate within the upper dermis. Intraepidermal lymphocytes arranged in

so-called Pautrier's collections are a common finding at this stage. Cytomorphologically, small pleomorphic (cerebriform) cells predominate.

In tumours of mycosis fungoides a dense, nodular or diffuse infiltrate is found within the entire dermis involving the subcutaneous fat. Epidermotropism may be lost.

**Large cell transformation**

In later stages, patients with mycosis fungoides usually develop lesions with many large cells (immunoblasts, large pleomorphic cells or large anaplastic cells).<sup>12-14</sup>

Tumours with a large cell morphology may or may not express CD30. Expression of the antigen does not have any prognostic significance in these patients. Large cell transformation of mycosis fungoides bears a poor prognosis and usually heralds the terminal stage of the disease.

**Immunohistology**

Mycosis fungoides is characterized by an infiltrate of T-helper memory lymphocytes (βF1<sup>+</sup>, CD3<sup>+</sup>, CD4<sup>+</sup>, CD5<sup>+</sup>, CD8<sup>-</sup>, CD45Ro<sup>+</sup>). Only α/β a minority of cases exhibit a T-suppressor (βF1<sup>+</sup>, CD3<sup>+</sup>, CD4<sup>+</sup>, CD5<sup>+</sup>, CD8<sup>+</sup>) γ/δ (βF1<sup>-</sup>, CD3<sup>+</sup>, CD4<sup>+</sup>, CD5<sup>+</sup>, CD8<sup>+</sup>) lineage, without clinical and/or prognostic differences. In late stages there may be a (partial) loss of pan-T-cell antigen expression.

Cytotoxic markers are negative in mycosis fungoides, but in late stages of the disease a cytotoxic profile of neoplastic cells may be observed, with positivity for TIA-1 and granzyme B. These cases should not be classified as cytotoxic lymphomas, but as tumour stage mycosis fungoides with cytotoxic phenotypes.

**Molecular genetics**

No specific abnormalities have been reported. Using cDNA microarray analysis, a signature of 27 genes, including oncogenes and other genes involved in the control of apoptosis, has been recently identified in cases of early- and late-stage mycosis fungoides.<sup>15</sup>

Rearrangement of the *TCR* gene is commonly found in plaques and tumours, but is present only in approximately 50% of the cases in early (patch) lesions.

**Clinical and histopathological variants**

Several clinical and/or histopathological variants of mycosis fungoides have been described (Table 2)<sup>16</sup> Patients with these variants of the disease often show also features of "classical" mycosis fungoides at other sites of the body.

**Table 2. Clinicopathologic variants of mycosis fungoides**


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Acanthosis nigricans-like mycosis fungoides
Angiocentric mycosis fungoides
Bullous (vesiculo-bullous) mycosis fungoides
Dyshidrotic mycosis fungoides
Erythrodermic mycosis fungoides
Follicular (pilotropic) mycosis fungoides
Granulomatous mycosis fungoides/ Granulomatous slack skin
Hyperpigmented mycosis fungoides
Ichthyosis-like mycosis fungoides
Interstitial mycosis fungoides
Invisible mycosis fungoides
Mucinous mycosis fungoides
Mycosis fungoides palmaris et plantaris
Mycosis fungoides with eruptive infundibular cysts
Mycosis fungoides with follicular mucinosis
Mycosis fungoides with large-cell transformation
Pagetoid reticulosis (Woringer-Kolopp)
Papular mycosis fungoides
Papuloerythroderma Ofuji
Perioral dermatitis-like mycosis fungoides
Pigmented purpura-like mycosis fungoides
Poikilodermatous mycosis fungoides
Pustular mycosis fungoides
Small-plaque parapsoriasis
Syringotropic mycosis fungoides
Unilesional (solitary) mycosis fungoides
Verrucous/hyperkeratotic mycosis fungoides
Zosteriform mycosis fungoides

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**Treatment**

The standard treatment of early lesions includes psoralens in association with UV-A irradiation (PUVA - psoralens and UVA), interferon  $\alpha$ -2a, retinoids, or a combination of these three modalities.<sup>17,18</sup> Several other treatments have been used in the past (and are still in use at present), including UV-B irradiation (or narrow-band UV-B - 311nm), and topical application of chemotherapeutic agents. In many cases, patients with localized patches of the disease can be treated also with local steroid ointments. The administration of total body irradiation, proposed by some authors as a first-line treatment, should probably be restricted to patients with mycosis fungoides in later stages.

In the last years, many new protocols have been introduced for treatment of early mycosis fungoides, including, among others, photodynamic therapy with 5-aminolaevulinic acid, new retinoids such as bexarotene (administered orally or topically), new chemotherapeutic drugs for topical use, and

immune response modifiers such as imiquimod. At present not enough data are available to evaluate the efficacy of these new modalities in terms of remission and recurrence rates.

In late stages, in addition to PUVA, retinoids and interferon  $\alpha$ -2a, conventional systemic chemotherapy, extracorporeal photopheresis and radiotherapy have been applied. Allogeneic stem cell transplantation has been performed in a few patients, and seems to be a promising treatment modality, perhaps with potential for cure thanks to the graft-versus-tumour response. However, toxicity is still very high, and it is unclear whether allogeneic stem cell transplantation should be considered a treatment option for early tumour-stage mycosis fungoides. New chemotherapeutic or immunological agents, including, among others, gemcitabine, fludarabine, pegilated doxorubicin, pentostatin, interleukin-12, DAB<sub>389</sub>-IL-2 fusion protein, vaccination, and trimetrexate, have also been used in a few patients. However, treatment of advanced (tumour stage) mycosis fungoides has remained unsatisfactory, and the disease usually progresses in spite of aggressive therapy.

**Prognosis**

Mycosis fungoides is a malignant lymphoma of low-grade malignancy with prolonged survival, and progression from the clinical stage of patches to those characterized by plaques, tumours, and extracutaneous spread usually takes place over many years or decades.<sup>1,2</sup> Development of plaques and/or tumours, or of large cell transformation, heralds the terminal stages of the disease (patients may survive several years with tumor-stage mycosis fungoides, though). As the disease arises more commonly in the elderly, however, most patients do never progress to plaque- or tumor-stage, and die of disease-unrelated causes. In fact, it has been estimated that only 15-20% of patients die of their disease.<sup>19</sup> However, a small subset of patients experience a more rapidly aggressive course with extracutaneous spread and death due to complications of the disease (usually sepsis or other severe infections). Moreover, a substantial subset of patients are middle-aged or young adults, and a few are children, thus a having higher risk of progression during their lifetime.

The most important prognostic parameters are stage at diagnosis, absence of complete remission after first treatment, age, race (prognosis is worse in Blacks, but this may be related also to different access to therapy).<sup>18</sup> No significant differences in survival have been observed between stages Ia and Ib (TNM classification), or between patients with tumours and erythroderma.<sup>18</sup> Once extracutaneous

spread takes place, prognostic parameters have no influence on survival, and prognosis is bad. The detection of a malignant clone in blood is an independent prognostic criterion, whereas the exact implications of the detection of a clone in the skin in early phases of the disease is yet unclear. Although the influence of the presence of follicular mucinosis on survival is yet debated, it certainly complicates treatment of these patients. Finally, analysis of histopathologic features of biopsy specimens of early mycosis fungoides failed to detect histological parameters that could help predict the progression (or absence of progression) of the disease.

Although most treatments are efficacious in early phases, and long-term remissions can be achieved, it is unlikely that cure can be obtained, with the possible exception of the solitary variants of the disease (life-long follow-up, however, should be suggested in these patients as well). The use of the PCR technique has been advocated for the detection of minimal residual disease after treatment, but the value of this method as a routine investigation should be confirmed by large studies.

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