# Mycosis fungoides and cutaneous T-cell lymphomas

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of T-cell lymphoproliferative disorders involving the skin. The majority may be classified as mycosis fungoides or Sézary syndrome.

## Classification

Classification of CTCLs by the World Health Organization (WHO) and the European Organisation for Research and Treatment of Cancer (EORTC):[1]

### Indolent clinical behaviour

- Mycosis fungoides.[2]
- Variants and subtypes of mycosis fungoides.
- Folliculotropic mycosis fungoides.
- Pagetoid reticulosis.
- Granulomatous slack skin.
- Primary cutaneous anaplastic large cell lymphoma (CD30+).
- Lymphomatoid papulosis (CD30+).
- Subcutaneous panniculitis-like T-cell lymphoma.
- Primary cutaneous CD4+ small or medium pleomorphic T-cell lymphoma.

### Aggressive clinical behaviour

- Sézary's syndrome.[3]

- Primary cutaneous natural-killer/T-cell lymphoma, nasal-type.
- Primary cutaneous aggressive CD8+ T-cell lymphoma.
- Primary cutaneous gamma/delta T-cell lymphoma.
- Primary cutaneous peripheral T-cell lymphoma, unspecified.

## How common are cutaneous T-cell lymphomas? (Epidemiology)[4]

CTCLs typically affect adults with a median age of 55-60 years; the annual incidence is about 0.5 per 100,000.

Mycosis fungoides, Sézary's syndrome and primary cutaneous peripheral T-cell lymphomas not otherwise specified are among the most important subtypes of the CTCLs. Mycosis fungoides is the most common type of CTCL, representing 44-62% of cases.

## Cutaneous T-cell lymphoma symptoms[4]

- Patches and plaques may affect any area of the skin but are often distributed asymmetrically in the bathing suit area - ie hips, buttocks, groin, lower trunk, axillae and breasts. Involvement of the scalp often causes alopecia.
- In its early stages, mycosis fungoides mimics many benign dermatoses. The cutaneous eruptions wax and wane.

- The skin disease generally progresses from:

    - **Patch phase (up to 15 cm across)**: flat, erythematous pink-brown macules that may have a fine scale, may be single or multiple and may be pruritic. In dark-skinned individuals, the patches may appear as hypopigmented or hyperpigmented areas. As patches become more infiltrative, they evolve into palpable plaques.
    - **Plaque phase**: tend to be raised, with fine scale, well demarcated, erythematous shapes with irregular borders. Annular patterns with central clearing and pruritus are common.
    - **Mycotic or tumour phase**: with later visceral involvement and infection as the skin turns into ulcerating, necrotic tumours.

## Differential diagnosis[5]

Early in the course of disease, skin lesions may be nonspecific, with a non-diagnostic biopsy result; hence, confusion with benign conditions is common. The most important differential diagnoses of the CTCLs include:[4]

- All kinds of dermatitis and eczema.
- Adverse drug reactions.
- Parapsoriasis.
- Psoriasis.
- Lichen planus.
- Morphea.
- Panniculitis.
- Folliculitis.
- Pityriasis lichenoides chronica.
- Pityriasis lichenoides et varioliformis acuta.
- Pigmented purpuric dermatoses.

- Vitiligo.
- Lymphomatoid papulosis.

## Investigations[6]

- LFTs: lactate dehydrogenase (LDH) is a marker of bulky or biologically aggressive disease. Abnormal transaminase values may indicate hepatic involvement.
- Uric acid: may be raised in aggressive disease.
- Consider HIV testing (but the vast majority of patients are HIV-negative).
- CXR.
- CT scan of the abdomen and pelvis: in patients with advanced disease (stage IIB to stage IVB) or in patients with clinically suspected visceral disease.
- Skin biopsy: for a definitive diagnosis, skin biopsy shows mycosis or 'Sézary cells' (convoluted lymphocytes), a band-like upper dermal infiltrate and epidermal infiltrations of neoplastic lymphocytes (Pautrier's abscesses). Multiple biopsies may be required before the diagnosis is certain.
- Bone marrow examination: only if the patient has proven blood or nodal involvement.
- Lymph node biopsy: if the nodes are palpable.

The diagnosis of early mycosis fungoides often needs integration of clinical, histological and molecular features, since it can be confused with benign eczematous skin disease. Algorithms are often used.[7]

## Associated diseases

The CTCLs comprise a heterogeneous group of entities. Indolent low-risk entities, including mycosis fungoides and Sézary's syndrome are distinguished from aggressive entities, including peripheral T-cell lymphoma and its variants and HTLV-1 associated acute T-cell leukaemia/lymphoma.[8]

### Sézary's syndrome[3]

Sézary's syndrome is a variant of mycosis fungoides, occurring in about 5% of cases, in which the patient has generalised erythroderma and more than 1000 per $mm^3$ atypical T lymphocytes circulating in the peripheral blood - Sézary cells - CD4+ T lymphocytes with a highly convoluted and bizarre morphological appearance. It is characterised by erythroderma, leukaemia, generalised lymphadenopathy and hepatosplenomegaly. It occurs most frequently in middle-aged males. Patients have a median survival of less than five years.

## Staging[6] [9]

- Primary tumour (T):
    - T1: eczematous patches, papules, or limited plaques <10% of the skin's surface.
    - T2: erythematous patches, papules or generalised plaques covering 10% or more of the skin's surface.
    - T3: tumours, one or more.
    - T4: generalised erythroderma.
- Nodes (N):
    - N0: no nodes.
    - N1: clinically abnormal peripheral lymph nodes (record nodes involved) but biopsy negative for CTCL.
    - N2: peripheral lymph nodes positive for CTCL - but not abnormal clinically.
    - N3: abnormal nodes - CTCL Bx positive.
- Distant metastasis (M):
    - M0: no visceral organ involvement.
    - M1: visceral involvement (with pathological confirmation).

- Staging of mycosis fungoides:
    - Stage IA: patchy or plaque-like skin disease involving less than 10% of the skin surface area.
    - Stage IB: patchy or plaque-like skin disease involving 10% or more of the skin surface area.
    - Stage IIB: tumours are present.
    - Stage III: generalised erythroderma.
    - Stage IVA1: erythroderma and significant blood involvement.
    - Stage IVA2: lymph node biopsy result shows total replacement by atypical cells.
    - Stage IVB: visceral involvement (eg, liver, lung, bone marrow).

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## Mycosis fungoides treatment[4] [10]

Mycosis fungoides and Sézary's syndrome are rarely curable; the goal of treatment is to control the disease while keeping toxic effects to a minimum. Topical and skin-directed treatments are recommended first, especially in the early stages of disease. More aggressive treatments may show improvement or clearance of lesions but may also result in more adverse effects and should therefore be considered with caution.[11]

- Symptomatic treatments: emollients or antipruritics in combination with specific topical and systemic treatment.

- Topical treatments:
    - Topical steroids.
    - Topical retinoids.
    - Topical chemotherapy - eg, nitrogen mustard or bischloroethylnitrosourea.
    - Ultraviolet B or ultraviolet A treatment, enhanced with psoralen and UVA (PUVA) or total body electron beam radiation in the patch or plaque phase. These modalities are also used in the tumour phase, combined with systemic therapies - eg, PUVA plus interferon. [12]
- Systemic treatment:
    - For patients who have relapsed or whose disease is refractory to topical treatments or who have tumours, erythroderma, or nodal or visceral disease.
    - Extracorporeal photopheresis (leukapheresis with PUVA treatment for the collected white blood cells and then reinfusion of treated cells).
    - Recombinant interferon alfa.
    - Of the chemotherapeutic agents, pentostatin, gemcitabine, doxorubicin and oral retinoids seem to be particularly effective. [13] Activity against CTCL has been shown at relatively lower doses with less myelosuppression. [14]
    - Bexarotene (an agonist at the retinoid X receptor) may be used for disease confined to the skin.
    - Combination chemotherapy: is generally not used because the infectious complications and short response duration outweigh the modest response rates (compared to other non-Hodgkin lymphomas). Increased survival is not demonstrated with the use of combination chemotherapy compared to sequential topical agents.

- Allogeneic haematopoietic stem cell transplantations are used for treating advanced stages of mycosis fungoides and Sézary's syndrome.

## Complications

- Infection.
- High-output cardiac failure.
- Anaemia of chronic disorders.
- Oedema.
- Secondary malignancies.
- Skin cancer, including melanoma.
- Colon cancer.
- Hodgkin's lymphoma.
- Non-Hodgkin's lymphomas.

## Prognosis[4]

CTCLs are lifelong disorders that recur after discontinuation of therapy, even in cases that do not progress. In spite of the introduction of several therapeutic options for CTCLs, the malignant cells have the propensity to infiltrate lymph nodes and peripheral blood vessels, resulting in debilitating states. Progression to tumour stage where the neoplastic cells spread to the lymph nodes and internal organs has been reported in less than 5% of cases with CTCL.

Late-stage mycosis fungoides is associated with increasing immunosuppression, and death most often results from systemic infection. Other causes of increased mortality include secondary malignancies (eg, higher-grade non-Hodgkin's lymphoma, Hodgkin's disease, colon cancer) and cardiopulmonary complications (eg, high output failure).

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## Further reading

- Mycosis Fungoides and the Sezary Syndrome; National Cancer Institute (US)
- Mycosis Fungoides; DermIS (Dermatology Information System)



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