# Cutaneous T-cell lymphoma: diagnosing subtypes and the challenges


## Abstract

Cutaneous T-cell lymphoma is a rare type of extranodal non-Hodgkin's lymphoma that primarily affects the skin. The uncertain pathogenesis and variable clinical presentation make the diagnosis and management of cutaneous T-cell lymphoma a challenge. Cutaneous T-cell lymphoma is a chronic, relapsing illness with treatment aimed at symptomatic relief and improving patient related quality of life.
Early-stage cutaneous T-cell lymphoma typically follows an indolent course, often being mistaken for benign dermatological conditions which can lead to a diagnostic delay. Advanced stage cutaneous T-cell lymphoma has a poor prognosis with significant morbidity. Accurate diagnosis and early involvement of a specialist team is paramount to ensure correct management and improved patient outcomes. Promising advances are being made to develop novel agents which could improve prognosis and quality of life. This article provides an overview of the two main subtypes of cutaneous T-cell lymphoma: mycosis fungoides and Sézary syndrome. Clinical presentation, histopathological correlation and diagnostic challenges are reviewed alongside example case studies.



**Key words: Cutaneous lymphoma; Mycosis fungoides; Sézary syndrome**

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## Introduction

Cutaneous T-cell lymphoma is a rare form of extra-nodal non-Hodgkin's lymphoma, classified by T-cell infiltration into the skin (Bagherani and Smoller, 2016). The exact aetiology is unknown but is thought to be multifactorial. Potential causative factors include a combination of gene dysregulation, bacterial and viral agents, ultraviolet light and chemical exposure (Ghazawi et al, 2019). From 2013 data, the incidence of cutaneous T-cell lymphoma in the UK was approximately 0.7 per 100 000, with a predominance in males and a peak age between 50 and 74 years of age (Gilson et al, 2019). The commonest types of cutaneous T-cell lymphoma are mycosis fungoides, Sézary syndrome and primary CD30 positive cutaneous lymphoproliferative disorders. The 2018 update of the World Health Organization-European Organisation for Research and Treatment Classification (Willemze et al, 2019) reported a significant number of rarer additional subtypes of cutaneous T-cell lymphoma. Each subtype has its own unique clinical, histopathological and genetic characteristics, treatment options and prognosis.

## Mycosis fungoides

Mycosis fungoides is the most prevalent subtype, accounting for up to 60% of all cutaneous T-cell lymphomas, with 10% being the folliculotropic subtype (Willemze et al, 2019). Mycosis fungoides has a long natural history, typically presenting on non-sun-exposed areas such as buttocks, axillae, trunk and upper thighs with persistent or slowly progressive skin lesions of variable shapes and sizes. It initially typically presents with patch-like disease which may evolve into thickened plaques, tumours and on rare occasions can progress to nodal or organ involvement (Figure 1). Not all patients will progress through the stages. Skin lesions in classic patch stage mycosis fungoides are irregular, erythematous and scaly and may show surface wrinkling or poikiloderma (a combination of atrophy, vascular


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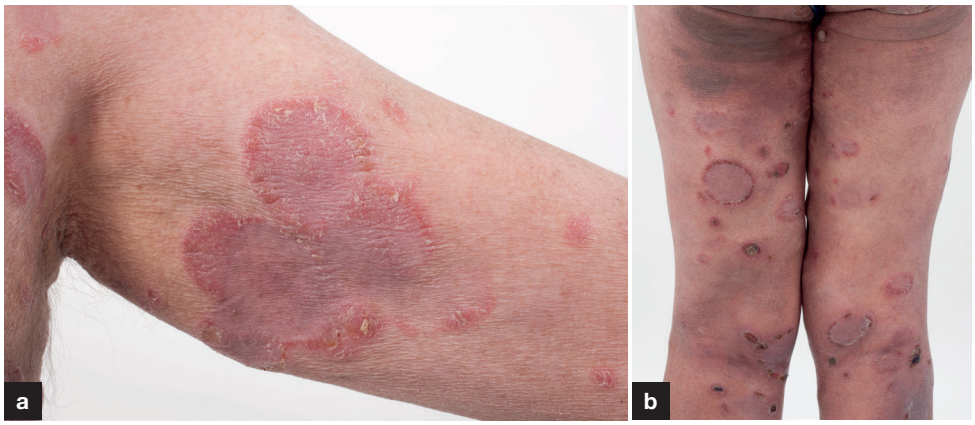


**Figure 1.** Plaque-like lesions, typical of mycosis fungoides, affecting (a) the upper and (b) lower limbs.

dilatation and hyperpigmentation). In non-Caucasian skin, patches may appear initially as hypo- or hyperpigmented patches without erythema.

## Sézary syndrome

Sézary syndrome is an aggressive leukaemic-phase type of cutaneous T-cell lymphoma accounting for <5% of cases. It is characterised by erythroderma (Figure 2), lymphadenopathy, predominantly in the axilla and inguinal regions, and blood involvement (B2) with ≥1000 circulating atypical lymphocytes defined as Sézary cells as per tumour nodal metastases (TNM) staging 2007. Blood involvement is determined using a manual Sézary cell count on a peripheral blood smear with B0 ≤ 5%, B1 >5% and B2 ≥1000 of the peripheral blood lymphocytes are atypical Sézary cells. More commonly, this is now determined by flow cytometry identifying Sézary cells as CD4 +ve CD 26 or CD 7 -ve.

CD30 lymphoproliferative disorders account for 20% of cases and are classified, based on their clinical presentation, as either lymphomatoid papulosis or primary cutaneous anaplastic large cell lymphoma.

## Natural history of cutaneous T-cell lymphoma

There is a clear demarcation between the natural history of early and advanced mycosis fungoides, with up to 25% of those with early disease progressing to advanced disease. In those with early stage mycosis fungoides (IA–IIA), disease is mainly confined to the skin (although the blood or lymph nodes can be involved) vs stages IIB–IV where skin tumours, lymph nodes and visceral organs are involved. While long-term follow-up studies with large prospective data are rare, clinical experience has shown that patients with stage 1A may have stable disease for decades, with the risk of disease progression within the first 10 years of diagnosis being <10% (van Doorn et al, 2000).

## Diagnosis of cutaneous T-cell lymphoma

### Clinicopathological correlation

Establishing a diagnosis of cutaneous T-cell lymphoma involves a multidisciplinary team of dermatologists, clinical oncologists, haematopathologists and dermatopathologists working closely in a specialist centre as defined by the current National Institute of Health and Care Excellence guidance (Gilson et al, 2019). The diagnostic pathway involves an accurate history, physical examination, medical photography and assessment of the total percentage of body surface area affected by skin lesions. This is known as the mSWAT score (modified severity weighted assessment tool). It is vital that diagnosis is arrived at following a careful clinicopathological assessment by a team with specialist expertise. Careful selection of the biopsy site by the clinician and dermatopathologist is recommended. The biopsy should be taken from the most indurated skin lesion and multiple biopsies may

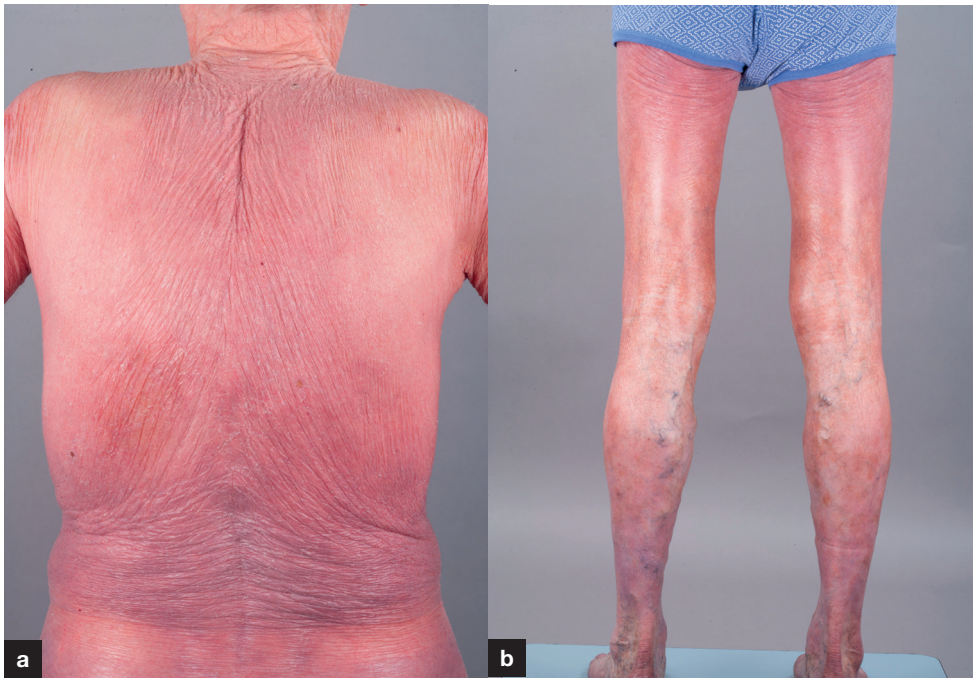


**Figure 2.** Areas of erythroderma on (a) the posterior torso and (b) lower limbs associated with Sézary syndrome.

be required. Immunohistochemical staining for pan T-cell antigens and molecular analysis for the presence of T-cell clones, gene rearrangement and CD30 positivity should also be performed. In the presence of erythroderma, a peripheral blood T-cell panel should be performed to assess the presence of Sézary cells and this is now recommended for all cases of cutaneous T-cell lymphoma as increased numbers of circulating aberrant T cells (B1; >250 cells <1000 cells per microlitre) can be seen in cases of earlier stage disease. However, the significance of this is not entirely clear.

## Histopathology of cutaneous T-cell lymphoma

There is a variable pattern of pathological findings which are not always diagnostic of cutaneous T-cell lymphoma. Typically, a predominance of CD4 positivity and loss of pan T-cell antigens (CD2, CD5 and CD7) is indicative of a diagnosis of mycosis fungoides. Other features include the presence of lymphocytes in the epidermis often tagging the basal keratinocytes, known as epidermotropism, either as single cells or as clusters known as Pautrier's microabscess, as shown in Figure 3. The presence of a T-cell clone on polymerase chain reaction is also found in mycosis fungoides but can in some cases be present in inflammatory lesions and in normal skin of the elderly population. However, the presence of identical clones from two different skin biopsy sites is strong evidence for mycosis fungoides and highlights the importance of taking multiple skin biopsies. In contrast to mycosis fungoides, intercellular oedema within the epidermis, known as spongiosis, with less extensive loss of CD5 and CD7, is common in reactive dermatoses. The pathological findings in patients with Sézary syndrome are similar but more subtle compared with mycosis fungoides, with less extensive epidermotropism and commonly loss of CD7 (>40%).

### CD30 positivity

CD30 positivity is present in all cases of CD30 lymphoproliferative disorders, and to a lesser extent in mycosis fungoides and Sézary syndrome. In addition to its diagnostic value, CD30 expression is important from a therapeutic perspective as it can be targeted for treatment with the anti-CD30 positive monoclonal antibody, brentuximab vedotin. Despite this, CD30 testing is not routine practice and there is currently no standardised method of testing or reporting a threshold of CD30 positivity. The CD30 positive expression is subject to sampling error and can be variable in different lesions within the same patient.

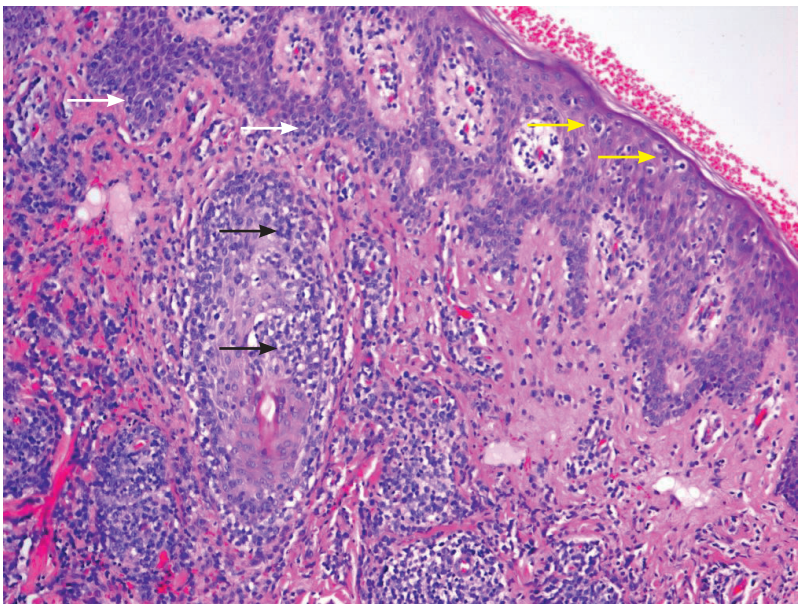

**Figure 3.** Histopathological findings of mycosis fungoides. Note the marked epidermotropism with tagging of the basal keratinocytes (white arrows) and collections of atypical lymphocytes forming Pautrier's microabscesses (yellow arrows). Folliculotropism (black arrows) is also present in this example.

## Diagnostic challenges of cutaneous T-cell lymphoma

The diagnosis of cutaneous T-cell lymphoma subtypes can be challenging for multiple reasons. The time from first presentation to diagnosis is variable but often delayed, with a median delay of 36 months (Scarisbrick et al, 2019). Establishing the correct diagnosis depends on the type and stage of disease and speciality of the responsible physician. The importance of early involvement of a specialist team and clinicopathological correlation, as highlighted in the current European Society of Medical Oncology guidelines (Willemze et al, 2018), should not be underestimated and is often one of the biggest diagnostic challenges to overcome. For example, in patients presenting to the correct specialist with obvious patch or plaque like disease a biopsy will be performed, while those with more subtle disease may miss out, resulting in a diagnostic delay.

## Example cases

### Case 1

The impact of early referral to the appropriate physician is highlighted in the first case of a 74-year-old woman who presented to her GP with an asymptomatic hypopigmented lesion in the inframammary breast tissues (**Figure 4**).

The location of the skin lesion within the breast tissue prompted an urgent referral to the local breast team. An incisional biopsy was performed and reviewed by the haematological malignancy diagnostic service, raising the suspicion of a lymphoma, and the patients was subsequently referred to a haematologist. A positron emission tomography computed tomography scan and bone marrow biopsy were also performed. Once at the specialist centre, review by a consultant dermatologist and dermatopathologist confirmed the diagnosis of benign morphoea. She was subsequently discharged with topical treatment if required under local dermatology follow up. This case highlights the unnecessary involvement of multiple specialities early in the patient pathway and inappropriate investigations, all of which resulted in increased anxiety and diagnostic delay for the patient.

In its earliest stages (IA–IIA), cutaneous T-cell lymphoma can mimic common inflammatory skin conditions such as eczema, psoriasis, drug-related reactions, chronic or atopic dermatitis, lichen planus and folliculitis. The clinical overlap between reactive dermatoses and cutaneous T-cell lymphoma can result in missed diagnoses and patients being inadequately treated. Patients may be treated for presumed eczema with skin-directed

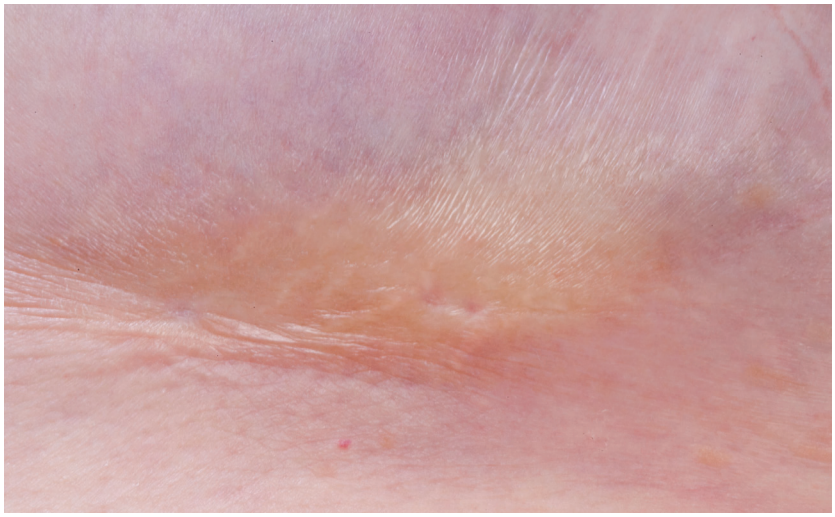

**Figure 4.** A hypopigmented yellowish shiny plaque lesion in the inframammary breast tissue.

therapies such as corticosteroids or light therapy without having a biopsy (Girardi and Edelson, 2000; Peterson et al, 2019). As the response to treatment is often temporary, a biopsy is thus performed; however, recent treatment can cause inaccurate pathological findings, further adding to the delay (Rodd et al, 2012). Close follow up with multiple interval biopsies may help establish the correct diagnosis in such cases. The lack of a single diagnostic test to confirm a diagnosis of cutaneous T-cell lymphoma and subtle histological features makes differentiation from benign disorders difficult (Kash et al, 2016). The delay increases the potential risk of progressive disease, and leads to a persistence of distressing symptoms, all of which can have a detrimental impact on the patient's quality of life.

### Case 2

The second case highlights the overlap and co-existence of reactive inflammatory skin conditions and underlying mycosis fungoides. A 39-year-old man presented with new nodular lesions on his trunk and limbs and more recently ulcerated lesions on his feet (**Figure 5a**). Before this he had been treated for a 10-year history of atopic eczema (**Figure 5b**) and contact dermatitis with topical therapies and ciclosporin. Multiple skin biopsies over a 5-year period from different sites were reported as showing reactive changes only. He was referred to a specialist centre and repeat biopsy from the tumours confirmed a diagnosis of mycosis fungoides. He was successfully treated with a combination of radiotherapy to sites of confirmed mycosis fungoides and psoralen ultraviolet A plus retinoids to the underlying eczema.

## Treatment of cutaneous T-cell lymphoma

The overall strategy for treatment of cutaneous T-cell lymphoma is to help patients live with their disease with optimum quality of life, focusing on symptomatic relief and local disease control with minimal treatment-related toxicity. In the UK, there is National Institute of Health and Care Excellence guidance regarding treatment of CD30-positive cutaneous T-cell lymphoma with brentuximab vedotin (National Institute of Health and Care Excellence, 2019) and on the use of mogamulizumab for previously treated mycosis fungoides and Sézary syndrome (National Institute of Health and Care Excellence, 2021). Mogamulizumab has also been approved by the Scottish Medicines Consortium in Scotland. There is no gold standard algorithm, partly because the main evidence consists of retrospective data from cohort studies and there is also a lack of prospective randomised controlled trials. Advances have been made to improve the patient pathway via published international guidelines by the British Association of Dermatologists and United Kingdom Cutaneous Lymphoma Group (Gilson et al, 2019) and European Society of Medical Oncology (Willemze et al, 2018).

The treatment of early-stage disease is with skin-directed therapy which includes topical corticosteroids, narrow band ultraviolet B or psoralen ultraviolet A. Topical chemotherapy using chlormethine gel (nitrogen mustard) is awaiting National Institute of Health and Care

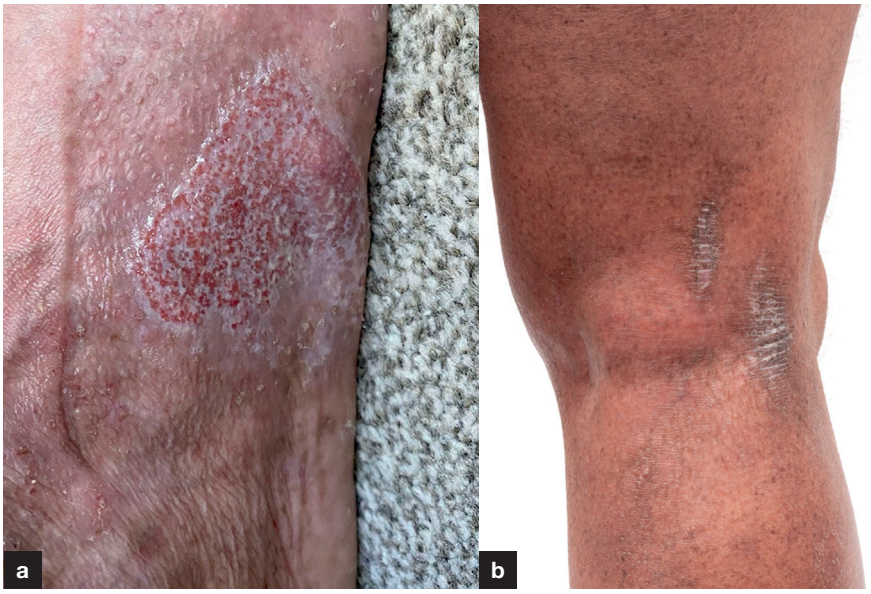


**Figure 5.** Similarities in appearance between mycosis fungoides and atopic eczema. a. An erythematous thick plaque or early tumour on the foot. b. A hyperpigmented lichenified eczematous lesion in the flexure.

Excellence approval in the UK. Radiotherapy can be used to treat symptomatic single target lesions, with total skin electron beam therapy reserved for those with more widespread skin disease. In advanced stage disease, first-line systemic options include interferon, methotrexate and retinoids, with targeted therapies and chemotherapy kept in reserve (Willemze et al, 2018). Treatment including chemotherapy options will be covered in an accompanying article. Sézary syndrome can be treated with extracorporeal photopheresis in a number of specialist centres in the UK. Extracorporeal photopheresis is a photoimmune therapy in which lymphocytes are removed from the blood, and exposed to psoralen and ultraviolet A before being returned to the patient. Allogeneic stem cell transplant can be used in selected cases of advanced disease to consolidate and achieve a durable remission.

The timing of when to initiate treatment can be difficult. In patients with early-stage asymptomatic disease, active monitoring can be used. Risk stratification of patients to understand which patients remain at an early stage and which may progress to advanced stage disease is challenging. It is estimated up to one third with early-stage disease will progress within 10 years to advanced stages (≥IIB). Identification of these patients will help improve prognosis and overall survival. The international Prospective Cutaneous Lymphoma International Prognostic Index trial is collecting prognostic data in patients with early-stage disease to improve management and survival in those at risk of disease progression (Scarisbrick et al, 2019). Symptoms and response to treatment can also be unpredictable, with patients often left feeling self-conscious and socially isolated with a poor quality of life. Ongoing clinical trials provide an exciting therapeutic landscape, with newer therapies becoming available that will hopefully improve patients' physical and psychological wellbeing.

## Conclusions

Cutaneous T-cell lymphoma is challenging for patients because of the rare nature of the condition. In its earliest stage, there is often a delay in diagnosis as a result of similarities with benign conditions, while in the more advanced stage patients experience considerable morbidity. To date there has been a paucity of data and effective treatments to improve disease control and quality of life. The landscape is changing, however, with successful international collaboration in clinical trials and new treatment approaches leading to improved patient outcome in the future.

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## Key points

- Cutaneous T-cell lymphoma is a rare disease with variable modes of presentation.
- Owing to the similarity in presentation with more common conditions, there is often a delay in diagnosis.
- Diagnosis and management should be carried out by a multiprofessional specialist team.

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### Conflicts of interest

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