Fast Facts: Diagnosing Cutaneous T-Cell Lymphoma

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Declaration of Independence
This book is as balanced and as practical as we can make it. Ideas for improvement are always welcome: feedback@fastfacts.com
Introduction

Although many cutaneous T-cell lymphomas (CTCLs) run a generally indolent clinical course, prompt and accurate diagnosis should be the rule, not the exception. In today’s changing environment of medical care, patients may have to wait to see a dermatologist, even one without expertise in CTCL, such that the challenge of swift and accurate diagnosis often lies with primary care providers and pathologists.

Without the correct history, description of lesions and clinical work-up, a clinicopathological correlation is difficult to reach. We have written this concise text specifically to help primary care providers, pathologists and general dermatologists recognize some of the clinical presentations, histopathological patterns and work-up needed for the diagnosis of CTCL.

The clinical presentation of CTCLs can vary greatly (many consider it one of the ‘great mimickers’) and the histopathology and ancillary molecular studies performed to assist in the diagnosis of CTCL can be difficult to recognize, analyze and interpret. Furthermore, the clinical behavior and treatment responses of primary cutaneous lymphomas are frequently very different to their nodal counterparts, making accurate diagnosis essential for management. Recognition of an atypical rash by the astute practitioner can lead to earlier biopsies. In turn, if given a strong clinical history, the pathologist can make informed decisions with respect to the histopathology findings under the microscope. This teamwork is the cornerstone of the robust clinicopathological correlation that is crucial to the diagnosis of CTCL.

All patients with mycosis fungoides, with the exception of those with the earliest stages of disease, should be referred to a dermatologist with a specialist interest in skin lymphoma. In addition, those with early-stage CTCL who fail to respond to skin-directed therapy should also be referred. In this book we provide a succinct basis for the understanding, diagnosis and work-up of CTCL by non-specialists, with the aim of improving collaboration between general clinicians and pathologists.
List of abbreviations

ALK: anaplastic lymphoma kinase
ATLL: adult T-cell lymphoma/leukemia
CBC: complete blood count
CCR: chemokine (C-C motif) receptor
CD: cluster of differentiation
CLA: cutaneous lymphocyte antigen
CTCL: cutaneous T-cell lymphoma
EBV: Epstein–Barr virus
EMA: epithelial membrane antigen
FMF: folliculotropic mycosis fungoides
HIV: human immunodeficiency virus
HTLV-1: human T-cell lymphotropic virus type 1
IFN: interferon
Ig: immunoglobulin
IL: interleukin
LDH: lactate dehydrogenase
LFT: liver function test
LyP: lymphomatoid papulosis
MF: mycosis fungoides
NK: natural killer (cell)
PC-ALCL: primary cutaneous anaplastic large cell lymphoma
PET/CT: positron emission tomography/computed tomography
SPTCL: subcutaneous panniculitis-like T-cell lymphoma
SS: Sézary syndrome
TCR PCR: T-cell receptor polymerase chain reaction
TGF: tumor growth factor
Th cell: T helper cell
TIA-1: T-cell intracellular antigen
WHO/EORTC: World Health Organization/European Organisation for Research and Treatment of Cancer
Over the past few years much work has been done in the field of cutaneous T-cell lymphoma (CTCL) in terms of the clinical, pathological, biological and etiologic understanding of this diverse group of diseases. Nevertheless, controversy still exists with respect to the classification, biology and behavior of these neoplasms. Further advances in research, technology and treatment will inevitably increase our understanding.

**Classification**

**WHO classification by type.** The term cutaneous T-cell lymphoma (CTCL) encompasses a wide range of disorders. The most common are mycosis fungoides (MF) and Sézary syndrome (SS), which account for approximately 65% of all CTCLs (Figure 1.1). CD30+ lymphoproliferative disorders, such as lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (PC-ALCL), make up around 25% of all CTCLs. The remaining 10% are the rarest of the CTCLs, and are listed in Table 1.1.

The atypical cells in CTCL are usually CD4+ T cells, but may be CD8+; the latter is more common in children but is also seen in some adults.

![Figure 1.1 Breakdown of classification of cutaneous T-cell lymphomas. LPD, lymphoproliferative disorders; MF, mycosis fungoides; SS, Sézary syndrome.](image-url)
### TABLE 1.1

**2008 WHO-EORTC classification of cutaneous NK/T-cell lymphomas (with 2016 WHO classification changes indicated by asterisks)**

- **Mycosis fungoides and variants**
  - folliculotrop tic
  - pagetoid reticulosis
  - granulomatous slack skin
- **Sézary syndrome**
- **Primary cutaneous CD30+ T-cell lymphoproliferative disorders**
  - lymphomatoid papulosis (types A–E, LyP with 6p25* rearrangement, and others)
  - primary cutaneous anaplastic large cell lymphoma
- **Subcutaneous panniculitis-like T-cell lymphoma**
- **Primary cutaneous gamma-delta (γ/δ) T-cell lymphoma**
- **Hydroa vacciniforme-like lymphoproliferative disorder**
- **Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma**
- **Primary cutaneous acral CD8+ T-cell lymphoma***
- **Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder***
- **Adult T-cell leukemia/lymphoma**
- **Peripheral T-cell lymphoma, NOS**
- **Extranodal NK/T-cell lymphoma, nasal type**

**Others with common cutaneous precursor lesions or secondary involvement**

- Blastic plasmacytoid dendritic neoplasm
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK+
- Anaplastic large cell lymphoma, ALK–*
- Breast implant-associated anaplastic large cell lymphoma*

*Updated in 2016 WHO classification from 2008 WHO classification.¹

ALK, anaplastic lymphoma kinase; CD, cluster of differentiation; EORTC, European Organisation for Research and Treatment of Cancer; LyP, lymphomatoid papulosis; NK, natural killer; NOS, not otherwise specified; WHO, World Health Organization.
When the malignant cells are CD8+, the clinical presentation may be of hypopigmented patches rather than scaly red patches. In 2005 and 2008, an extensive classification of CTCL was published by the World Health Organization (WHO). However, following research advances in biological and clinical behavior, the advisory committee recently released the initial 2016 Revision of the WHO Classification of Lymphoid Neoplasms; the final version of this classification is expected later in 2016. Although this revision contains minimal alterations to the 2008 classification (see Table 1.1), it helps to further define this group of diseases.

**Classification by clinical behavior.** Clinicopathological correlation is crucial to the correct diagnosis of CTCL. However, the cytomorphology of T cells often does not correlate with the clinical behavior of the lymphoma, except in rare instances. Clear communication between pathologists and clinicians is needed to combine their knowledge of the clinical behavior with their awareness of the histological and clinical mimics of CTCL, all of which must be carefully reviewed before a definitive diagnosis is established.

Most T-cell lymphomas can be classified into two broad categories: aggressive (fast growing) or indolent (slow growing) (Table 1.2). The most common CTCLs are discussed below, and the pathology is reviewed in more detail in Chapters 3 and 4.

**Indolent CTCLs** generally have a good prognosis and prolonged course, and often lack systemic symptoms. They are usually treated with skin-directed therapies. A number of these patients will progress to advanced/aggressive disease (around 25% of patients with MF) with a higher risk of secondary malignancies, particularly in those with LyP who may develop a systemic lymphoma. As such, all patients with indolent CTCL should be followed up closely for development of lymphadenopathy or systemic symptoms such as fever, weight loss or night sweats suggestive of systemic lymphoma or another cancer type.

**CTCLs with intermediate/indeterminate clinical behavior** include advanced stages of MF (stages IIB–IV), Epstein–Barr virus (EBV)-associated T- and natural killer (NK)-cell lymphoproliferative disorders and a subset of other NK/T-cell disorders that are rare
and less well understood at this time. For example, hydroa vacciniforme-like lymphoproliferative disorder has been found to be associated with chronic active EBV infection in pediatric patients. Although it tends to have an indolent course, the disease does progress in some patients, who have an aggressive projection with fevers, hepatosplenomegaly and systemic involvement. \(^2,3\) Prospective and retrospective studies are continuing to evaluate and further categorize these conditions.

**Aggressive CTCLs** often progress rapidly with extracutaneous involvement, have a poor prognosis and are associated with systemic symptoms. These CTCLs warrant systemic treatment and generally display a cytotoxic immunophenotype. However, both CTCLs with indolent behavior and benign dermatoses (i.e. vitiligo, lichen planus)
can also display a cytotoxic immunohistochemical profile. Therefore, diagnosis cannot be based on a cytotoxic profile alone, again illustrating the need for clinicopathological correlation for these diseases.

**Epidemiology**

**Incidence.** CTCLs are relatively rare diseases, with an annual age-adjusted incidence of 6.4 per million persons in the USA and similar worldwide.\(^4\) In the USA, the incidence of MF and non-MF has been reported to be 4.5 and 4.0 per million persons, respectively.\(^5\) One study reported a general increase in incidence of \(2.9 \times 10^{-6}\) per decade between 1973 and 2002, while another reported a relatively stable incidence between 1998 and 2009.\(^6\) Several studies have shown geographic clustering of incidence within the USA, suggesting that environmental or other external etiologic factors have a role in the cause of the disease.\(^7,8\)

**Age, sex and ethnicity.** In recent years, the Surveillance, Epidemiology and End Results (SEER) databases in the USA have been used to analyze the age-adjusted incidence and survival rates in individuals with CTCL by sex and ethnicity.\(^9\) CTCL primarily presents in white individuals in the sixth decade of life, although the highest incidence in this population is seen in 70–79 year-olds.\(^4,7\) African-American patients present with CTCL at a younger age than white patients (mean age of 51.5 vs 59.2 years). While the incidence of CTCL rises sharply with age, it also occurs in pediatric and young adult populations.

The overall incidence of both MF and non-MF CTCL is higher in men than women (Figure 1.1a), with a ratio of 2.2 to 1. African-Americans have a higher incidence of both MF and non-MF than whites, Asian/Pacific islanders and Native Americans (Figure 1.1b). Furthermore, African-Americans and hispanics have a statistically significant greater incidence of presenting at a more advanced stage of both MF and non-MF.\(^5,7\)

**Mortality and survival.** Mortality from MF is 0.0064 per 100 000 person-years and is higher in men than women. Advanced age and
black race are associated with poorer survival. Overall, 5-year survival rates for patients with CTCL are high (85%), ranging from 91% for patients with MF to 40% for patients with SS.

**Etiology**

Little is known of the etiology of MF. A possible causal role for human T-cell lymphotropic virus type 1 (HTLV-1) provirus was indicated in 1980, when it was found in the peripheral blood of a black patient with cutaneous lymphoma. Subsequently, marked geographic
clustering of the HTLV-1 provirus was found in countries where HTLV-1 is endemic, such as Japan, the Caribbean basin and South America, and it has since become clear that HTLV-1 is associated with adult T-cell lymphoma/leukemia (ATLL), a systemic lymphoma distinct from MF/SS.

Epidemiological studies have found an increased incidence of secondary internal malignancies in patients with CTCL, particularly lung carcinoma, colonic adenocarcinoma and non-Hodgkin’s lymphoma, which do not appear to be related to therapy.¹¹ MF is also associated with other lymphomas of both T-cell (LyP, nodal CD30+ anaplastic large cell lymphoma) and B-cell (Hodgkin’s disease, chronic lymphocytic leukemia) origins. Furthermore, in some patients with a secondary T-cell neoplasm, the same T-cell clone has been identified in both lymphomas, indicating that they are derived from the same neoplastic clone.

There does not appear to be a familial link in CTCL; however, there are reports of an increase in lymphoma in first-degree relatives of patients with CTCL.
Key points – classification, epidemiology and etiology

- Mycosis fungoides (MF) and Sézary syndrome (SS) account for approximately 65% of cutaneous T-cell lymphomas (CTCLs); lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (PC-ALCL) make-up 25%, and the remaining 10% are rare diseases.
- Clinicopathological correlation is crucial in the diagnosis of CTCLs, as the histological findings do not always correspond with the clinical behavior, and many benign dermatoses can mimic the histopathology of MF and other CTCLs.
- CTCL is generally subdivided into neoplasms with indolent and those with aggressive clinical behavior. Indolent forms have a good prognosis and prolonged course, and often lack systemic symptoms. They are usually treated with skin-directed therapies. Aggressive forms have a poor prognosis, and are associated with systemic symptoms that warrant systemic treatment. They generally display a cytotoxic immunophenotype.
- CTCL is a relatively rare group of diseases with an estimated incidence of 6.4 per million persons.
- Onset most often occurs around the sixth decade of life in white people, with earlier onset in African-Americans.
- African-Americans have statistically significant higher incidence of both MF and non-MF CTCL, and often present with more advanced disease.
- Patients with CTCL have an increased risk of secondary malignancies.
- No familial link in CTCL has been identified.
References


The skin is the second most frequent extranodal site, after the gastrointestinal tract, for lymphoma, with an annual incidence of 0.5–1 cases per 100 000 people. Primary cutaneous lymphomas are defined as lymphomas without evidence of extracutaneous spread. They can be divided into primary cutaneous T-cell lymphoma (CTCL) and B-cell cutaneous lymphoma. CTCL are a rare group of T-cell malignancies primarily involving the skin.

**Mycosis fungoides**

**Early disease.** About 70% of patients with classic mycosis fungoides (MF) present with erythematous scaly patches (Figures 2.1–2.3) or plaques (Figures 2.4 and 2.5) in a ‘sun bathing suit’ distribution on non-sun-exposed sites (i.e. hips, buttocks, groin, lower trunk, axillae and breasts). Early lesions may resolve when exposed to sunlight.

![Figure 2.1](image)

Figure 2.1 Erythematous scaly patches of mycosis fungoides, presenting in a ‘bathing suit distribution’ over the buttocks. The annular patches may appear very similar to patches of eczema, psoriasis or tinea corporis.
Clinical presentation and differential diagnosis

Because of the difficulty in diagnosing MF, patients are often treated for eczema or psoriasis for months to years before the correct diagnosis is made. Hypopigmented MF is more common in children and black skin, and the malignant T cells are more frequently CD8+. These early-stage lesions consist of atypical T lymphocytes that

Figure 2.2 Patches of mycosis fungoides scattered over the trunk; the same T-cell clone is found within these patches.

Figure 2.3 (a) Scaly patches of mycosis fungoides on the upper arm. These patches may thicken, and are termed plaques when palpable and elevated above surrounding normal skin. (b) High power view of patch showing erythema and scaling.
infiltrate the skin and show affinity for the epidermis (epidermotropism) (see Chapter 3). Some patches may become infiltrative and evolve into raised well-demarcated plaques.

In addition to the physical disfigurement associated with these skin lesions, patients with MF experience itching (pruritus) and pain, which generally worsens in more advanced disease, all of which has a

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**Figure 2.4** (a) A plaque of mycosis fungoides covering the posterior thigh. (b) A high power view of this plaque showing elevation above the surrounding normal skin, which is indicative of a deeper infiltrate of atypical lymphocytes than is seen in patches.

**Figure 2.5** Patches and plaques frequently occur together in the same patient as seen here on (a) the arm and (b) the trunk.
negative effect on quality of life. Patients with limited patches and plaques (covering less than 10% of the body surface area) may have near-normal survival. About 25% of patients will progress to advanced disease, with survival of 10–25 years.

**Advanced disease.** About 30% of patients with MF develop tumors (Figures 2.6–2.11) or erythroderma (Figures 2.12 and 2.13). Patients with these late-stage lesions tend to have rapidly progressive disease and a poor survival of 1–4 years, with spread to lymph nodes or internal organs (viscera).

**Figure 2.6** Patches and tumors may occur together in the same patient as seen here on (a) the buttocks and (b) the face.
Figure 2.7 Tumor on the wrist with ulceration.

Figure 2.8 A domed tumor on the right arm. These tumors often show large cell transformation whereby normal medium-sized mycosis fungoides cells become large and blast-like. This carries a poor prognosis.

Figure 2.9 Domed tumors on (a) the scalp and (b) forehead.
Figure 2.10 Folliculotropic tumors. These have a predilection for the head and neck. Atypical cells infiltrate the follicular epithelium and cause alopecia.

Figure 2.11 A large ulcerating tumor on the right cheek. Sometimes the tumors increase in size so rapidly that they become necrotic rather than domed (see Figure 2.9).
Variants of mycosis fungoides

*Folliculotrop mycosis fungoides* (FMF) is the term used when the patient presents with follicular lesions, i.e. patches, plaques or tumors with follicular accentuation (Figures 2.14 and 2.15). These folliculotropic lesions may present with cysts, comedones (Figure 2.16) or milia (Figure 2.17), often with a predilection for the head and neck.
The histology of these lesions shows atypical lymphocytes infiltrating the hair follicles (see Chapter 3). Alopecia may occur; in fact, the combination of facial plaques and eyebrow alopecia is pathognomonic of FMF (Figure 2.18). Folliculotropic MF may present with lesions limited to patches of MF showing follicular accentuation +/- alopecia, +/- cysts, or with thick plaques and/or tumors with follicular accentuation often showing a predilection to the head and neck. Patients with lesions limited to follicular patches may have a similar

**Figure 2.14** Mycosis fungoides (MF) patch with follicular accentuation, as seen in folliculotropic MF.

**Figure 2.15** Mycosis fungoides plaques with follicular accentuation, as seen in folliculotropic MF.
prognosis to classical MF whilst those with dense follicular plaques have a poorer prognosis similar to those with advanced tumor stage classical MF.

*Pagetoid reticulosis* is a variant of MF that presents as a solitary patch or plaque, usually located on the extremities and acral sites. It rarely progresses and has a good prognosis.
Clinical presentation and differential diagnosis

Granulomatous slack skin is a subtype of MF that presents with redundant folds of skin, typically in the flexor sites.

Sézary syndrome

Sézary syndrome (SS) is a form of CTCL that presents as advanced disease with erythroderma (Figure 2.19), lymphadenopathy and peripheral blood involvement. This leukemic form of CTCL is typically aggressive with a median survival of just 3 years. Patients experience extreme pruritus and often succumb to infection. The face may become infiltrated with atypical lymphocytes, resulting in thickening of the facial skin folds, the characteristic leonine facies.

Figure 2.18 Patches and plaques on the head with eyebrow alopecia may be considered pathognomonic of folliculotrophic mycosis fungoides.

Figure 2.19 Erythroderma as part of Sézary syndrome. There is moderate infiltration of the skin with atypical lymphocytes, equivalent to plaque mycosis fungoides.
Nail dystrophy is often striking (Figure 2.21) and can affect both the hands and feet, as can hyperkeratosis. Ectropion is a common finding in these patients as well.

The combination of painful pruritic skin lesions, which may be cosmetically disfiguring, and an incurable disease, can severely negatively affect quality of life. Emotional support is critical.

**Other less common variants of indolent primary CTCL**

Primary cutaneous anaplastic CD30+ large cell lymphoma (PC-ALCL) presents with rapidly enlarging skin tumors, often with central
necrosis (Figure 2.22). PC-ALCL typically occurs in the seventh decade but there are reports in adolescence and young adulthood. The prognosis is usually good, with 5-year survival rates of more than 90%. Systemic spread rarely occurs, but relapses in the skin are common.

Lymphomatoid papulosis (LyP) is a self-resolving form of primary CD30+ CTCL that usually occurs in early adulthood. It presents with recurrent nodules and papules, typically less than 1 cm in diameter, at distant sites that become necrotic before resolving to form an atrophic scar (Figure 2.23). All subtypes of LyP have an almost identical clinical presentation, but the histology is varied (see Chapter 4).

Adult T-cell leukemia/lymphoma (ATLL) is a T-cell neoplasm associated with the human T-cell leukemia virus 1 (HTLV-1).

**Figure 2.22** CD30+ primary cutaneous anaplastic large cell lymphoma (PC-ALCL). Lesions of PC-ALCL rarely resolve completely without treatment and tumors may enlarge quickly. Partial spontaneous resolution may occur, notably after skin biopsy.

**Figure 2.23** Papulonecrotic lesions of lymphomatoid papulosis over the upper back. The white atrophic scars are from self-healing lesions.
It most commonly presents as erythroderma, widespread papules and plaques and papular erythroderma.

**Subcutaneous panniculitis-like T-cell lymphoma** (SPTCL) is divided into those derived from $\alpha\beta$ T cells and those from $\gamma\delta$ T cells. Given their clinical, prognostic and immunophenotypic differences these are now considered two separate entities: SPTCL and primary cutaneous $\gamma\delta$ T-cell lymphoma.

*SPTCL* is an indolent disease that is confined to the subcutis, presenting as solitary or multiple nodules and plaques. Although skin recurrences frequently occur, extracutaneous spread is rare.

**Primary cutaneous $\gamma\delta$ T-cell lymphoma** has an aggressive clinical course, usually with systemic spread, and may be complicated by a hemophagocytic syndrome. Systemic symptoms such as fever, fatigue and weight loss may be present. The malignant cells have a cytotoxic immunophenotype.

**Other CTCL variants** are included within the WHO/EORTC cutaneous lymphoma classification.

*Extranodal natural killer (NK)/T-cell lymphoma, nasal type,* is nearly always positive for Epstein–Barr virus (EBV), with an aggressive clinical course. It usually presents as a destructive midfacial tumor or as multiple plaques or tumors with ulceration on the trunk or extremities. Systemic symptoms and a hemophagocytic syndrome may be present.

**Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder** typically presents with a small solitary dermal tumor on the face, neck or upper trunk, and has a favorable clinical course.

**Primary cutaneous peripheral T-cell lymphoma, unspecified,** includes all those cutaneous T-cell lymphomas that do not fit into any of the better-defined subtypes of CTCL.

**Differential diagnosis**

Early-stage lesions may be misdiagnosed as common dermatoses or fungal infections, such as:

- discoid eczema
- atopic eczema
Clinical presentation and differential diagnosis

- psoriasis
- tinea corporis
- lichen planus.

MF should be suspected if lesions do not respond to conventional treatment. Other indicators for a diagnosis of MF include the distribution of lesions over the buttock area or specific features such as poikiloderma (telangiectasia, atrophy, dyspigmentation) (Figures 2.24 and 2.25), follicular lesions including cysts, comedones and patches/plaques with follicular accentuation, or hyperpigmented (Figure 2.26) or hypopigmented patches (Figure 2.27).

**Figure 2.24** Poikilodermatous mycosis fungoides (MF) consists of patches showing telangiectasia, atrophy and dyspigmentation. This variant of MF may be distributed extensively over the body but is frequently associated with a good prognosis.

**Figure 2.25** Poikilodermatous patches of mycosis fungoides in a bathing suit distribution.
Most forms of cutaneous lymphoma have a nodal counterpart: systemic nodal lymphomas may involve the skin during the disease course and, on occasions, may present with skin involvement. As systemic lymphomas require different treatments to cutaneous lymphomas, it is essential that all cases, except early-stage MF, are given a full investigative work-up, including a CT scan, to exclude secondary cutaneous involvement from a systemic lymphoma.

Insect bites can mimic PC-ALCL and LyP.
Clinical presentation and differential diagnosis

Key points – clinical presentation and differential diagnosis

- Cutaneous T-cell lymphomas (CTCL) are a rare group of lymphomas that affect the skin.
- Mycosis fungoides (MF) is the commonest type of CTCL and typically presents in the early stages with patches and plaques.
- Early-stage MF may progress to advanced disease with skin tumors and blood involvement, with lymph node or visceral spread. Some patients (30%) present with advanced disease.
- Early-stage MF has an excellent prognosis and long survival (10+ years), whilst the advanced stages are rapidly progressive in 1–4 years.
- Sézary syndrome is the erythrodermic form of CTCL that presents in advanced disease with leukemic blood involvement.
- Cutaneous lymphomas may be CD30+, and this group forms a spectrum from lymphomatoid papulosis with relapsing and remitting lesions to large cell anaplastic lymphomas that may grow rapidly. These types of CTCL have an excellent prognosis and should be differentiated from transformed MF, which also has large atypical CD30+ cells.
- Other forms of CTCL are rare and include subcutaneous panniculitis-like lymphoma, extranodal natural killer/T-cell lymphoma and primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder.

References


Adaptive immunity
The immune system comprises two branches: the innate and adaptive immune response. The innate system has no memory, so both the initial and subsequent responses to antigens are similar. The adaptive immune system involves the concept of memory such that when a lymphocyte interacts with an antigen, it triggers a downstream cascade of immune mechanisms that then lead to a faster and stronger immunologic response to subsequent encounters with antigens. B lymphocytes (B cells) and T lymphocytes (T cells) are the major players in the adaptive immune system. Here, we focus on the immunologic role of the T cell.

T-cell pathophysiology
T cells arise from lymphoid progenitor cells in the bone marrow and mature within the thymus. The T-cell receptor (TCR), a molecule on the surface of the T cell, is formed through gene rearrangement of the four TCR genes: α, β, γ and δ. The TCR is composed of two different gene pairs, either α and β or γ and δ (Figure 3.1), which interact with the antigen. Overall, the majority of clonal lymphocytes leading to various cutaneous T-cell lymphomas (CTCLs) have an α/β phenotype; however, certain, usually clinically aggressive, CTCLs have a γ/δ phenotype. Mature T cells are further subdivided into T-helper (Th) cells and T-suppressor cells. Th cells express CD4, while T-suppressor cells express CD8.

Aside from the aforementioned CD4 and CD8 clusters of differentiation (CD), numerous other immunophenotypic markers/antibodies are used to help provide information for the classification and diagnosis of CTCLs (Table 3.1). A number of recent studies support immunophenotyping even in early disease to assist in the understanding of treatment-specific options. This is particularly important as we move further into the age of targeted therapeutics.
### Table 3.1

**Antibodies used in the diagnosis of cutaneous T-cell lymphomas**

<table>
<thead>
<tr>
<th>Antigen/antibody</th>
<th>Immunologic function/phenotype/specificity</th>
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<tbody>
<tr>
<td>CD1a</td>
<td>Precursor T cells, Langerhans cells</td>
</tr>
<tr>
<td>CD2</td>
<td>T cells</td>
</tr>
<tr>
<td>CD3</td>
<td>T cells</td>
</tr>
<tr>
<td>CD4</td>
<td>T-helper cells</td>
</tr>
<tr>
<td>CD5</td>
<td>T cells (present in some B-cell leukemias/lymphomas)</td>
</tr>
<tr>
<td>CD7</td>
<td>T cells</td>
</tr>
<tr>
<td>CD8</td>
<td>T-suppressor/cytotoxic cells</td>
</tr>
<tr>
<td>CD10</td>
<td>Follicular T-helper cells, germinal center cells</td>
</tr>
<tr>
<td>CD25</td>
<td>α chain of IL-2R; associated with ATLL</td>
</tr>
<tr>
<td>CD30</td>
<td>Activated T cells (also present in activated B cells, Hodgkin cells)</td>
</tr>
<tr>
<td>CD45</td>
<td>Leukocyte common antigen</td>
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**CONTINUED**
Malignant CD4+ T cells produce Th2 cytokines, leading to decreased Th1 function, elevated immunoglobulin (Ig) E and eosinophil levels, and reduced delayed type IV hypersensitivity. These activated T cells can also inhibit cell-mediated immunity by producing tumor growth factor (TGF)-β and interleukin (IL)-10. Over time, the levels of myeloid cells, plasmacytoid dendritic cells, cytotoxic CD8+ T cells and CD56+ natural killer (NK) cells decrease, leading to a monoclonal population.

While some of the pathophysiology of mycosis fungoides (MF) and Sézary syndrome (SS) overlaps, it has now been shown that the T-cell subsets for these two diseases are distinct, resulting in treatment-
specific outcomes. It is therefore important to distinguish erythrodermic MF from SS (Table 3.2).

**Mycosis fungoides**
Table 3.3 summarizes the pathophysiology, histopathology, immunophenotype and clonality of MF, as discussed in more detail below.

**Pathophysiology.** MF lacks the lymph-node homing molecules chemokine (C-C motif) receptor type 7 (CCR7) and L-selectin, and the differentiation marker CD27. Conversely, CCR4 and cutaneous lymphocyte antigen (CLA) are strongly expressed, which is a phenotype of skin-homing resident effector memory T cells. CLA, the ligand for E-selectin, is expressed on endothelial cells, and chemokine (C-C motif) ligands 17 and 22 (CCL-17 and CCL-22) assist in cutaneous trafficking. The subsequent CCL-17/CCR4 ligand/receptor interaction signals the recruitment of epidermotropic lymphocytes.

**Histopathology.** Given the significant number of clinical and histological mimics of MF, good clinicopathological correlation

<table>
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<tr>
<th>TABLE 3.2</th>
<th>Pathophysiology of mycosis fungoides and Sézary syndrome</th>
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<tbody>
<tr>
<td>MF</td>
<td>SS</td>
</tr>
<tr>
<td>Increased Th2 function</td>
<td>Increased Th2 function</td>
</tr>
<tr>
<td>– elevated IL-4, IL-5, IL-10, TGF-β</td>
<td>– elevated IL-4, IL-5, IL-10, TGF-β</td>
</tr>
<tr>
<td>Phenotype: resident effector memory T cells</td>
<td>Phenotype: central memory T cells</td>
</tr>
<tr>
<td>Expresses CCR4 and CLA</td>
<td>Expresses CCR7/L-selectin and CD27</td>
</tr>
</tbody>
</table>

CCR, chemokine (C-C motif) receptor; CD, cluster of differentiation; CLA, cutaneous lymphocyte antigen; IL, interleukin; TGF, tumor growth factor; Th2, T helper cell 2.
### TABLE 3.3
**Typical diagnostic characteristics of mycosis fungoides**

#### Pathophysiology
- Strongly expresses CCR4 and CLA
- Skin-homing resident effector memory T-cell phenotype

#### Histopathology
- Small- to medium-sized epidermotropic T lymphocytes with cerebriform/pleomorphic nuclei
- ± Pautrier’s microabscesses
- Haloed lymphocytes along the dermal–epidermal junction
- Papillary dermal fibrosis
- Dense, diffuse infiltrate with larger, more atypical lymphocytes in plaque and tumor stage
- Large cell transformation ≥ 25% of large pleomorphic, anaplastic or immunoblastic cells

#### Immunophenotype
- CD2+, CD3+, CD4+, CD5+/-, CD7-, CD8-, CD45RA-, CD45RO+, TCR-β+
- ± CD30 in large cell transformation

#### Clonality
- Monoclonal T-cell population by TCR PCR
- Matching clones from separate sites more diagnostically informative

CCR4, chemokine (C-C Motif) receptor 4; CLA, cutaneous lymphocyte antigen; TCR PCR, T-cell receptor polymerase chain reaction.

is essential for accurate diagnosis in this disease. However, the histopathology of MF can vary greatly, especially with the differing clinical presentations of patches, plaques and tumors (see Chapter 2). In general, MF is characterized by small- to medium-sized T lymphocytes with cerebriform/pleomorphic nuclei within the epidermis, known as epidermotropism (Figure 3.2). The most
specific finding tends to be intraepidermal collections of lymphocytes known as Pautrier’s microabscesses (Figure 3.3). These are rare in early-stage MF, but common in plaque-stage disease.4–6

*Early patch-stage disease* is most often composed of a patchy lichenoid dermal infiltrate, lymphocytes tagging along the dermal–
epidermal junction, basal layer lymphocytes with perinuclear halos and fibrosis of the papillary dermis (Figures 3.4–3.6). Epidermotropic lymphocytes, especially those larger than dermal lymphocytes, are a helpful diagnostic clue. However, these may be absent if recent topical

Figure 3.4 Patch-stage mycosis fungoides with epidermotropism and papillary dermal fibrosis (×200).

Figure 3.5 A lichenoid band-like infiltrate is common in the patch stage of mycosis fungoides (×100). Inset shows higher-powered view of infiltrate with atypical T cells in the epidermis (×200).
treatments have been initiated (Figure 3.7). Caution must be taken to avoid overcalling epidermotropic lymphocytes in areas of spongiosis, which is a common finding in inflammatory diseases. In inflammatory processes, this is best described as exocytosis of lymphocytes rather than epidermotropism, given the ‘buzz word’ association of the latter with MF. Haloed lymphocytes are also helpful in differentiating inflammatory diseases from MF. Furthermore, Langerhans cells and eosinophils are not an uncommon histological finding in MF.

**Plaque-stage disease.** The lichenoid infiltrate is more dense and continuous in this later stage of disease (Figures 3.8 and 3.9)
Figure 3.8 A more dense superficial infiltrate of malignant T cells in the plaque stage of mycosis fungoides (×40). Inset shows higher-powered view of the infiltrate (×400).

Figure 3.9 A more dense dermal infiltrate of atypical T cells from a patient presenting with plaques (×100). Note the lack of epidermotropism, which can occur in both plaque- and tumor-stage mycosis fungoides.
compared with the patchy infiltrate seen in earlier stages of MF. Pautrier’s microabscesses are usually more readily identified (see Figure 3.3).

*Tumor-stage disease* is characterized by a dense, nodular to diffuse, dermal lymphocytic infiltrate that can extend into the subcutis (Figure 3.10). Epidermotropism may be lost, and the lymphocytes can be much more varied in size and shape (Figure 3.11). Large cell transformation (i.e. cells that are more than 4 times the size of a normal lymphocyte) has been detected in up to 50% of patients with advanced-stage tumors.\(^8\) By definition, large cell transformation is present if more than 25% of the dermal infiltrate is composed of large pleomorphic, anaplastic or immunoblastic cells (Figure 3.12). Large cell transformation may be either CD30+ or CD30-, with the latter portending a poorer prognosis (Figure 3.13).\(^9\) The differential

**Figure 3.10** The tumor stage of mycosis fungoides is characterized by a dense, diffuse, malignant lymphocytic infiltrate that extends toward the subcutis (×20).

**Figure 3.11** Hyperchromatic, enlarged and pleomorphic T cells from a mycosis fungoides tumor-stage biopsy (×400).
diagnosis would also include primary cutaneous anaplastic large cell lymphoma (PC-ALCL), therefore clinical history is needed in order to establish this diagnosis. However, PC-ALCL is defined by the presence of 75% or more CD30+ anaplastic cells, and IRF4 translocations occur in PC-ALCL.10

**Other histological patterns of mycosis fungoides** have been recognized, including perivascular infiltrates, spongiosis, interface dermatitis, interstitial pattern, granulomatous dermatitis and pigmented purpuric-like dermatitis, further proving the need for good communication between the clinician and the pathologist.
Pseudoepitheliomatous hyperplasia is seen in both MF and CD30+ lymphoproliferative diseases. Caution must be taken not to overdiagnose these biopsies as squamous cell carcinomas (Figure 3.14).

Variants of mycosis fungoides

*Folliculotropic mycosis fungoides*, as the name suggests, is characterized by infiltration of neoplastic lymphocytes in the follicular epithelium (Figure 3.15). The characteristic epidermotropic infiltrate seen in the patch and plaque stage of the disease (see Figure 3.2) may or may not be present in the folliculotropic variant. Follicular mucinosis – prominent mucin deposition that disrupts the follicular architecture – may be present (Figure 3.16). This term has been associated with non-neoplastic conditions, but it is generally felt to be most closely associated with MF. Prominent perifollicular eosinophils and granulomas may be present. The destruction of the follicular units leads to clinically recognized alopecia, often termed alopecia mucinosa. Folliculotropism has been known to indicate a worse prognosis and should therefore be included in pathology reports. Syringotropism (Figure 3.17) is common and should be reported if present, prompting the clinician to avoid superficial or topical treatments for this variant.

*Figure 3.14* Pseudoepitheliomatous hyperplasia in mycosis fungoides, which is commonly misdiagnosed as squamous cell carcinoma (SCC) (x40).
Figure 3.15  Horizontal histological sections of folliculotrophic mycosis fungoides from a scalp biopsy, showing (a) perifollicular lymphocytic infiltrates (×20). (b) shows atypical lymphocytes displaying follicular epithelial infiltration, akin to ‘epidermotropism’ of the follicle (×200).

Figure 3.16  (a) Disrupted follicle with infiltrating lymphocytes (×100). (b) shows higher-powered view of the disrupted follicle in which notable mucin deposition is present, consistent with follicular mucinosis (×400).

Figure 3.17  Mycosis fungoides with syringotrophic infiltration of malignant cells (×400).
**Pagetoid reticulosis** shows epidermal hyperplasia with prominent epidermotropism (Figure 3.18) and, most commonly, a cytotoxic CD8+ phenotype. Syringotropism can occur in pagetoid reticulosis as well.

Pagetoid reticulosis strongly warrants clinicopathological correlation, as the histological findings described above are also seen in the indolent disorder lymphomatoid papulosis (LyP), type D, and the clinically aggressive diseases cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, cutaneous γ/δ T-cell lymphoma and extranodal NK/T-cell lymphoma, nasal type. However, in pagetoid reticulosis the malignant cells are present almost exclusively in the epidermis, whereas in the other mentioned conditions, dermal involvement occurs as well.

**Granulomatous slack skin** is very rare. Histopathology demonstrates a diffuse dermal and often subcutaneous infiltrate of neoplastic T cells with histiocytic granulomas composed of giant cells, frequently with intracellular lymphocytes. Again, clinical correlation is required to make this diagnosis, as the granulomatous variant of MF cannot be differentiated based on histological findings alone.

**Immunophenotype.** The typical immunophenotype of MF is CD2+, CD3+, CD4+, CD5+/-, CD7-, CD8-, CD45RA-, CD45RO+, TCR-β+ (Figure 3.19). Although most cases of MF are CD7-, many inflammatory diseases that clinically mimic MF are also CD7-. Therefore, care must be taken in interpreting this marker. Generally,

![Figure 3.18](image-url)

*Figure 3.18* Acral skin with psoriasiform hyperplasia, demonstrating epidermotropic T lymphocytes in a pagetoid pattern (×100).
an increased CD4:CD8 helper:suppressor ratio and a CD8:CD3 ratio of less than 25% in the epidermis supports the diagnosis of MF.\textsuperscript{11}

CD8+ predominant cytotoxic cases also exist (Figure 3.20). These include CD8+ MF with a cytotoxic phenotype as well as the somewhat controversial entity of hypopigmented MF. Early-stage MF can present with CD8+ predominance in up to 20% of cases. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL), cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, and $\gamma/\delta$ T-cell lymphoma are also CD8+ predominant conditions. Furthermore, the cytotoxic markers T-cell intracellular antigen (TIA)-1, granzyme-B and perforin are positive in these cases. However, these markers can

Figure 3.19 Immunophenotyping of atypical T lymphocytes in mycosis fungoides: (a) CD3+; (b) CD4+ (present in the dermis but generally sparing the epidermal component); (c) CD8- (×200).

Figure 3.20 CD8+ atypical T cells in the epidermis, consistent with CD8+ predominant mycosis fungoides (×100).
also be positive in indolent diseases such as MF, LyP, PC-ALCL and SPTCL. Clinical correlation is necessary to rule out the clinically aggressive cytotoxic lymphomas.

**Laboratory work-up** for MF depends on the stage of the disease, as well as institutional and provider preferences. A complete blood count (CBC) may reveal eosinophilia; it has been observed in 20–25% of patients with MF, secondary to the secretion of Th2 cytokines by neoplastic cells, and is associated with a worse prognosis and disease progression. Lactate dehydrogenase (LDH) is another serological marker that has been associated with a negative prognosis, though it is non-specific and can be elevated in non-neoplastic conditions. Other serological tests, such as liver function tests (LFTs) and metabolic panels, are generally ordered as the treatment regimen advances to systemic agents with known systemic side effects. Testing for HIV and human T-cell lymphocytic virus 1 (HTLV-1) should be considered if the patient is from an endemic area, has notable risk factors or has a clinical presentation of erythroderma.

In early patch-stage disease, a clinical assessment of body surface area and lymph node examination is generally all that is needed for staging (see Chapter 5). Some authorities perform flow cytometry even in patients with patch-stage disease, though others feel this is not necessary. If lymph nodes are fixed, clustered and/or greater than 1.5 cm, a nodal biopsy is warranted.

In early patch-stage disease, the histology results and clinical presentation will determine whether a subsequent systemic work-up should be performed. On the other hand, patients with plaques, tumors and erythroderma should undergo a full systemic work-up, including CBC, LDH, ultrasonography of suspected enlarged lymph nodes, CT or positron emission tomography (PET-CT) of the chest, abdomen and pelvis, and flow cytometry (discussed in further detail below). A bone marrow biopsy should also be considered.

**Sézary syndrome**
Table 3.4 summarizes the diagnostic criteria in terms of the pathophysiology, histopathology, immunophenotype and clonality of SS.
### TABLE 3.4

**Diagnostic criteria in Sézary syndrome**

**Clinical presentation**
- Erythroderma, defined as erythema covering at least 80% of body surface area

**Pathophysiology**
- CCR7 and CD27 are expressed in comparison to MF, which does not express CCR7 and CD27
- Th2 cytokine profile with expression of IL-4, IL-5, IL-10
- Central memory T-cell phenotype

**Histopathology**
- Small- to medium-sized epidermotropic T lymphocytes with cerebriform nuclei
- ± Pautrier’s microabscesses
- Sometimes less dense lymphocytic infiltrate and/or lack of epidermotropism compared to MF; though monotonous dermal infiltrates do occur
- > 1000/mm³ Sézary cells in circulation (see Figure 3.21)

**Immunophenotype**
- CD3+, CD4+, CD7-, CD8-, PD-1+, CD10+, BCL-6+, CXCL-13+
- Flow cytometry demonstrating:
  - Increased CD4+ cells with a CD4+:CD8+ ratio > 10:1
  - CD4+:CD7- ratio ≥ 40%
  - CD4+:CD26- ratio ≥ 30%
- Loss of T-cell antigens (CD2, CD3, CD4, CD5)

**Clonality**
- Monoclonal T-cell population by TCR PCR
- Clonal TCR rearrangement in the blood and/or matching monoclonal population in the skin and peripheral blood

CCR7, chemokine (C-C Motif) receptor 7; IL, interleukin; MF, mycosis fungoides; TCR PCR, T-cell receptor polymerase chain reaction; Th2, T helper cell 2.
Pathophysiology. As with MF, SS displays a Th2 phenotype; however, it expresses CCR7, L-selectin and CD27, as well as CCR4 (see Table 3.2). This phenotype is associated with central memory T cells. The transcription factors GATA3 and JunB are overexpressed, and decreased levels of interleukin (IL)-12, interferon (IFN)-α, and IFN-γ lead to decreased Th1 function.

Histopathology of SS can be very difficult to interpret. It can only be distinguished from MF when diagnosed alongside the clinical picture. Like MF, patchy lichenoid infiltrate, lymphocytic epidermotropism with cerebriform nuclei (‘Sezary cell’, Figure 3.21) and Pautrier’s microabscesses (see Figure 3.3) are evident. Although the histopathology in SS can be similar to that of MF, there is often less of, or even a lack of, epidermotropism and less lymphocytic infiltrate, which makes the diagnosis even more challenging (Figures 3.22 and 3.23). Moreover, the clinical differential diagnosis of erythroderma includes inflammatory disorders such as psoriasis, pityriasis rubra pilaris, atopic dermatitis, contact dermatitis and seborrheic dermatitis, all of which can have overlapping features not only with SS but also erythrodermic MF.

Figure 3.21 (a) Electron micrograph of a multilobed ‘Sézary cell’. (b) An example blood smear of a ‘Sezary cell’. Part (a) reproduced with kind permission of Professor Rein Willemze, Leiden University Medical Center.
Immunophenotype. As mentioned previously, unlike MF, SS cells have a central memory T-cell phenotype associated with CCR7/L-selectin and CD27, and a Th2 cytokine profile with expression of IL-4, IL-5 and IL-10. Although SS has a similar T-helper immunoprofile to MF (i.e. CD3+, CD4+, CD7-, CD8- on formalin fixed paraffin embedded tissues), in contrast to MF, SS is also associated with a T-follicular helper phenotype (PD-1+, BCL-6+, CXCL-13+). Interestingly, T-follicular helper phenotypes are also associated with other systemic T-cell processes such as angioimmunoblastic T-cell lymphoma and some peripheral T-cell lymphomas.¹²⁻¹⁴
Pathology and diagnosis of mycosis fungoides and Sézary syndrome

Laboratory work-up. By definition, patients with SS are at an advanced stage of disease and a complete systemic work-up must be performed. Besides a clinical examination, this should include CBC, Sézary cell count, LDH, CT or PET-CT, flow cytometry, T-cell receptor polymerase chain reaction (TCR PCR) (see below), lymph node biopsy and, if necessary, a bone marrow biopsy. Patients with erythroderma should be screened for HIV and HTLV-1. Flow cytometry is also a beneficial and commonly used test, not only for diagnosis but also for monitoring treatment response, including in patients enrolled in clinical trials. As with all CTCLs, interpretation of the data must include clinical correlation.

Molecular testing

T-cell receptor polymerase chain reaction. To date, the use of TCR PCR to identify monoclonal rearrangements of lymphocytes has been a mainstay of practice (although some authors feel it should not be used in early disease). Up to 80–90% of cases of MF are shown to have clonal populations for β and/or γ genes (Figure 3.24), although this may only be 50–60% in early disease. However, T-cell clonality is not specific to MF. Autoimmune disorders and other inflammatory processes can also have clonal T-cell populations. Distinguishing between CTCL and inflammatory disorders has a sensitivity of 78% and specificity of 74%. Other pitfalls of TCR PCR include difficulty in interpreting oligoclonal peaks and clonal heterogeneity, false negative results due to primer annealing and other technical issues, and false positive results due to preferential amplification with limited lymphoid populations. For these reasons, duplicate analyses are recommended to identify definitive clonality.

TCR PCR can be particularly helpful if the histopathology is non-diagnostic or if there is a clinicopathological mismatch. Finding matching clones in separate cutaneous biopsies and/or blood samples is very beneficial in diagnosing the more clinically and histologically challenging cases.

Finding clonality on TCR PCR is particularly crucial to diagnosis and prognosis when determining if a lymph node has tumor involvement or whether it is dermatographic/reactive in nature.
Figure 3.24 Two examples of a T-cell receptor polymerase chain reaction (TCR PCR) report. Each example shows a β (upper graph) and γ (lower graph) chain. Two different sites were submitted for both patient 1 and 2. In patient 1, there is a monoclonal dominant peak around 304 bp that is present not only in both the β and γ reads at biopsy site 1, but also the same dominant peaks at 304 bp are found at biopsy site 2. These findings show a positive monoclonal rearrangement at multiple sites, and in the correct clinical and histological setting this would be consistent with a diagnosis of mycosis fungoides (MF).
Figure 3.24 continued In patient 2, site 1 shows polyclonal non-matching peaks. In site 2, the $\beta$ chain (upper graph) is polyclonal. Although it appears the peaks between the $\beta$ and $\gamma$ chains match, when one looks closely, these are actually at different base pair regions (~260 bp on the $\beta$, and 200 bp on the $\gamma$). The findings in patient 2 illustrate a polyclonal, non-matching TCR PCR which is not suggestive of a diagnosis of MF.
It is also crucial in the diagnosis of SS, although clonal studies may be negative in early SS and the presence of a ‘benign’ positive TCR clone in the peripheral blood of an elderly individual can occur. With this in mind, the presence of matching clones in the blood and skin are more diagnostically informative and specific for a diagnosis of SS.

Next generation sequencing/high throughput sequencing (NGS/HTS) may eventually replace TCR PCR, although it is too early to know for certain. A recent study showed that this platform more accurately diagnosed all stages of CTCL and, perhaps more importantly, helped to distinguish CTCL from benign inflammatory conditions. The decrease and eradication of clonal populations seen on NGS/HTS has also been used to identify treatment response. Multiple centers are studying this platform for use in earlier diagnosis, and to enhance understanding of the pathophysiology of CTCLs and the role of targeted therapeutics in these malignancies.

Reflectance confocal microscopy is also being studied as a tool to assist in diagnosis; however, further studies are needed to validate the clinical potential for this modality.

Molecular genetics
Given the complexity of study findings and lack of overall uniform data, attempts to establish a genetic and molecular basis for MF/SS have been challenging. With both overlapping and unique genetic discoveries for MS and SS, there is still uncertainty as to whether MF with blood involvement is a separate entity to SS. For this reason, the molecular genetics of both diseases are discussed here.

Genetic and epigenetic studies have shown changes in methylation, pathway dysregulation, chromosomal aberrations, and expression differences in numerous cytokines that relate to apoptosis, T-cell activation, DNA damage repair and chromatin remodeling. The nuclear factor-κB signaling pathway is one of the most recognized and well-studied pathways in MF/SS pathogenesis, and numerous upstream regulators have been found to be associated with this enhanced signaling. In both MF and SS, other notable findings include activation
of the STAT3/STAT5 and IL-2 receptor genes, dysregulation of FAS, chromosomal gains on 1q, 7p and 7q, and chromosomal losses on 5q, 9p and 13q. In MF, upregulation of microRNA (miR)-155 and downregulation of miR-203 and miR-205 have been noted, while in SS, miR-21 is upregulated and miR-342 is downregulated.

Oncogene and tumor suppressor gene alterations of MYC, CDKN2A/p16, p53 and PTEN have been identified in advanced disease; however, no differences in prognosis in cases of MF/SS with these mutations have been identified yet, except for a known reduced survival in patients with CDKN2A deletions in transformed MF. Recent findings have shown recurrent mutations in the GATA-3, AIRD1A, DNMT3A, ZEB1 and RAG genes, which are already well known in systemic T-cell lymphomas; T-cell activation/regulation further implicates these genes. A novel CTLA4-CD28 fusion oncogene has also been identified in simultaneous studies in MF/SS.

With continued advances in research and clinical technology, there is hope for improved understanding of the implications of these findings in this complex disease.
Key points – pathology and diagnosis of mycosis fungoides and Sézary syndrome

• With all cutaneous T-cell lymphomas (CTCLs), histopathology and clinical correlation is crucial in reaching the diagnosis.
• Malignant T cells in mycosis fungoides (MF) are derived from skin-homing resident effector memory T cells, while in Sézary syndrome (SS), the malignant cells are derived from central memory T cells.
• Both MF and SS usually display a CD3+, CD4+, CD7-, CD8- immunophenotype; however, CD8+ predominant cases of MF do exist.
• Histopathology of MF is characterized by small- to medium-sized T lymphocytes with epidermotropic cerebriform/pleomorphic nuclei, Pautrier's microabscesses, haloed lymphocytes along the dermal–epidermal junction and papillary dermal fibrosis.
• Tumor-stage MF has a more dense, diffuse and nodular infiltrate of atypical lymphocytes and can lack epidermotropism.
• Large cell transformation can occur in plaque- and tumor-stage disease. These cells are more than 4 times the size of a normal lymphocyte and must account for more than 25% of the atypical infiltrate. They can be either CD30+ or CD30-, with the latter leading to a poorer prognosis.
• Patients with early patch-stage MF generally do not need full systemic work-up; however, patients with plaque- and tumor-stage MF and SS need complete systemic work-up performed for staging.
• T-cell receptor polymerase chain reacton (TCR PCR) is a useful ancillary test in the diagnosis of MF, SS and other CTCLs. It is not 100% specific; however, in the correct clinical and histopathological setting it can be useful in determining monoclonality of the malignant lymphocytes. Matching clones identified from different samples are more useful in the diagnosis.
Pathology and diagnosis of mycosis fungoides and Sézary syndrome

References


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Primary cutaneous CD30+ lymphoproliferative disorders

Histologically, this group of cutaneous T-cell lymphomas (CTCLs) is characterized by varying degrees of CD30 expression, a cytokine belonging to the tumor necrosis receptor family. These disorders are low-grade indolent processes and often spontaneously regress. To date, it is unclear why these particular diseases confer a good prognosis, but it has been suggested that CD30+ may be related to tumor regression and/or apoptotic control.

Lymphomatoid papulosis. Although many variants have been described,1 the histological subtypes of lymphomatoid papulosis (LyP) recognized by the updated 2016 revision of the WHO classification of lymphoid neoplasms are discussed here (Table 4.1).

The varying subtypes show significant diagnostic overlap and, to date, no prognostic value has been derived from differentiating them.

The diagnostic work-up for LyP is generally limited to an initial complete blood count (CBC), lactate dehydrogenase (LDH) and metabolic panel. However, up to 20% of patients with LyP may present with or subsequently develop other lymphomas such as mycosis fungoides (MF), primary cutaneous anaplastic large cell lymphoma (PC-ALCL), Hodgkin lymphoma or other hematologic malignancies;2 further laboratory work-up and imaging is needed if systemic signs and symptoms are present or develop.

The immunophenotype for LyP is generally CD3+, CD4+, CD8-/+ , CD30+. CD5, CD7, CD15, CD26, anaplastic lymphoma kinase (ALK) and epithelial membrane antigen (EMA) are negative. While T-cell receptor polymerase chain reaction (TCR PCR) monoclonality has been demonstrated in approximately 50% of cases, there is no prognostic association with positivity. IRF4 translocations have also been identified; however, these are much more often associated with cutaneous PC-ALCL.
### Table 4.1

**Subtypes of lymphomatoid papulosis**

<table>
<thead>
<tr>
<th>Moniker</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
<th>Type D</th>
<th>Type E</th>
<th>Lyp w/ 6p25</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Classic/ conventional</td>
<td>MF-like</td>
<td>ALCL-like</td>
<td>Epidermotropic CD8+ cytotoxic TCL-like</td>
<td>Angiortropic/ angiodestructive</td>
<td>N/A</td>
</tr>
<tr>
<td>Cell type</td>
<td>Large, anaplastic ‘Reed–Sternberg-like’</td>
<td>Small, cerebriform</td>
<td>Large, anaplastic</td>
<td>Small, cerebriform</td>
<td>Variable</td>
<td>Epidermis: small, cerebriform Dermis: large, anaplastic</td>
</tr>
<tr>
<td>Pattern</td>
<td>Wedge</td>
<td>Wedge, lichenoid, epidermotropic</td>
<td>Nodular, sheets</td>
<td>Extensive epidermotropism</td>
<td>Variable with angiotropism</td>
<td>Variable</td>
</tr>
<tr>
<td>Immunology</td>
<td>CD3+, CD30+</td>
<td>CD3+, CD4+, CD8-, CD30+/</td>
<td>CD3+, CD30+</td>
<td>CD3+, CD4-, CD8+, CD30+, CD45RO+</td>
<td>CD3+, CD30+, rare CD56+, EBER1-</td>
<td>CD3+, CD30+ DUSP22-IRF4 rearrangement</td>
</tr>
<tr>
<td>Differential diagnoses</td>
<td>Arthropod bites, PLEVA</td>
<td>Mycosis fungoides (papular variant)</td>
<td>ALCL, transformed MF</td>
<td>Pagetoid reticulosis, aggressive epidermotropic CD8+ cytotoxic TCL</td>
<td>Cytotoxic T-cell lymphomas</td>
<td>Transformed mycosis fungoides, ALCL</td>
</tr>
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ALCL, anaplastic large cell lymphoma; MF, mycosis fungoides; PLEVA, pityriasis lichenoides et varioliformis acuta.
**Type A (classic/conventional)** is the most common histological subtype of LyP. Histopathology shows a wedge-shaped infiltrate of large, atypical, anaplastic CD4+, CD30+ T cells, sometimes with morphological similarities to Reed–Sternberg cells. Epidermotropism may or may not be present. Often, a mixed infiltrate of eosinophils, neutrophils and histiocytes is present (Figure 4.1).

**Type B (mycosis fungoides-like).** As suggested by the ‘MF-like’ pattern, LyP type B biopsies show either a wedge-shaped or lichenoid infiltrate of CD3+, CD4+, CD8-, CD30-, small- to medium-sized cerebriform lymphocytes. Epidermotropism is also usually present. Clinical correlation is needed to distinguish LyP type B from MF (Figure 4.2).

**Type C (ALCL-like),** like type A, is characterized by large, atypical, anaplastic CD30+ T cells with a mixed inflammatory infiltrate. However, rather than a wedge-shaped infiltrate, this subtype demonstrates nodules and sheets of anaplastic cells, as seen in

**Figure 4.1** Lymphomatoid papulosis, type A, ‘classic’, with characteristic wedge-shaped lymphocytic infiltrate (×40). Inset shows CD30+ clusters of activated T lymphocytes (×200).
PC-ALCL. Clinical correlation is necessary for a definitive diagnosis (Figure 4.3).

**Type D (cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma-like)** is characterized by CD3+, CD4-, CD8+, CD30+ markedly epidermotropic cerebriform T cells with a lichenoid or wedge-shaped dermal infiltrate (Figure 4.4). This histological pattern can be seen in both pagetoid reticulosis and cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. However, CD30+ is generally not seen in either of these differential diagnoses, so demonstration of CD30+ T cells with clinical correlation is crucial.
for diagnosis of this histological mimic. CD45RO can also be a helpful marker, as this is generally negative in cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.

**Type E (angiotropic/angiodestructive)** is characterized by large, anaplastic CD4+/−, CD8+/−, CD30+ and, rarely, CD56+ T cells in a wedge-shaped, lichenoid or diffuse pattern with notable angiotropism. Extravasated erythrocytes and vascular necrosis are prominent features. This pattern can mimic natural killer (NK)/T cell lymphoma, nasal type, and other cytotoxic lymphomas, but LyP type E always demonstrates in situ hybridization negativity for Epstein–Barr virus-encoded RNA-1 (EBER-1).

**Lymphomatoid papulosis with rearrangement of 6p25.** Although monoclonality has been identified in lesions of LyP, recurrent mutations are rare. However, a variant of LyP has recently shown recurrent rearrangements of the DUSP22-IRF4 locus on 6p25. This has led to recognition of a separate subtype in the revised 2016 WHO classification. The histopathology shows small, cerebriform
T cells in the epidermis with larger, atypical, anaplastic CD30+/- T cells in the dermis. Although the histological pattern overlaps with transformed MF, all lesions regress spontaneously.³

**Primary cutaneous anaplastic large cell lymphoma** is recognized as a separate entity to nodal ALCL, because of the good response PC-ALCL has to treatment and good prognosis. Microscopically, PC-ALCL is composed of dense, diffuse sheets of CD30+ anaplastic T lymphocytes that make up 75% or more of the neoplastic infiltrate (Table 4.2; Figures 4.5–4.7). Because lesions are commonly ulcerated, a mixed inflammatory infiltrate of neutrophils, eosinophils and histiocytes may be present as well.

Like LyP, the immunophenotype of PC-ALCL is generally CD3+/-, CD4+, CD8-, CD30+, with loss of CD5 and CD7. MF with CD30+ large cell transformation is also composed of CD30+ T cells (see Table 4.2). Clinical correlation is therefore crucial for the accurate diagnosis of PC-ALCL. Other differential diagnoses include LyP

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<th>PC-ALCL</th>
<th>MF with CD30+ LCT</th>
<th>Nodal ALCL</th>
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<tbody>
<tr>
<td>Diffuse sheets of CD30+ anaplastic T cells (≥ 75%)</td>
<td>Nodules to diffuse CD30+ anaplastic T cells (&gt; 25%)</td>
<td>Diffuse sheets of CD30+ anaplastic T cells</td>
<td></td>
</tr>
<tr>
<td>Usually EMA and ALK-1 negative</td>
<td>EMA and ALK-1 negative</td>
<td>EMA positive, ALK-1 positive/negative</td>
<td></td>
</tr>
<tr>
<td>IRF4 rearrangements occur</td>
<td>Lacks IRF4 rearrangements and t(2;5)</td>
<td>Characteristic chromosomal t(2;5)</td>
<td></td>
</tr>
<tr>
<td>Good prognosis</td>
<td>Poor prognosis vs MF without LCT</td>
<td>Poor prognosis</td>
<td></td>
</tr>
<tr>
<td>± spontaneous regression</td>
<td>No spontaneous regression</td>
<td>Systemic treatment necessary</td>
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ALK-1, anaplastic lymphoma kinase 1; C-ALCL, cutaneous anaplastic large cell lymphoma; EMA, epithelial membrane antigen; LCT, large cell transformation; MF, mycosis fungoides.
Pathology and diagnosis of non-mycosis fungoides CTCL

**Figure 4.5** Dense, diffuse, deep lymphocytic infiltrate of large, hyperchromatic, pleomorphic T cells in cutaneous anaplastic large cell lymphoma (×20 and ×200).

**Figure 4.6** (a) Large, highly atypical anaplastic-appearing lymphocytes in cutaneous anaplastic large cell lymphoma (×400). (b) Anaplastic T cells are the ‘hallmark’ cells of ALCL and resemble a horseshoe shape (×400).

**Figure 4.7** (a) Large, anaplastic T cells with CD30+ staining in cutaneous anaplastic large cell lymphoma (×200). (b) Sheets of CD30+ enlarged, pleomorphic T cells in PC-ALCL (×400).
type C and nodal ALCL. Histologically, PC-ALCL is generally EMA and ALK-1 negative compared with systemic disease. However, ALK-1 negativity does not rule out nodal disease, and ALK-1+ and EMA+ PC-ALCL have been reported.

Unlike patients with LyP, patients with clinical and histological findings for PC-ALCL must undergo full systemic work-up consisting of CBC, LDH, metabolic panel, HIV test and full body CT or PET-CT. Though not specific, molecular rearrangements in DUSP22-IRF4 are more common in PC-ALCL than in MF with large cell transformation. This translocation has also been identified in ALK-1-negative ALCL and LyP with 6p25 rearrangement. The WHO also recognizes ALK-1-positive and ALK-1-negative nodal ALCL as separate entities, given the differing prognostic significance – this is another reason for ensuring full systemic work-up in patients with suspected PC-ALCL.

Primary cutaneous small/medium CD4+ T-cell lymphoproliferative disorder
Previously categorized as a lymphoma, this entity was recently revised in the 2016 WHO classification of lymphoid neoplasms. Several studies have shown indolent behavior, successful conservative management and lack of recurrent mutations; it is therefore best managed as a lymphoproliferative disorder with unknown malignant potential. Many feel this entity is a variant of cutaneous lymphoid hyperplasia with clonality. Systemic work-up is not needed in patients with localized lesions.

Pathology illustrates a dense, diffuse dermal infiltrate of small- to medium-sized pleomorphic CD4+ T cells (Figures 4.8 and 4.9). These T cells also demonstrate a T-follicular helper phenotype with positivity for PD-1; they also sometimes express CXCL13, BCL-6 and CD10. An admixture of reactive B cells is common. Reactive germinal centers and granulomas may be seen as well.

Subcutaneous panniculitis-like T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is another difficult disease entity to diagnose purely on histopathology, as there is significant histological overlap with lupus panniculitis and primary
cutaneous γ/δ lymphoma (Table 4.3). Plasma cells, mucin and reactive histiocytes are reported in both SPTCL and lupus panniculitis, though many feel these findings are much more suggestive of lupus panniculitis.

Figure 4.8 Primary cutaneous small/medium CD4+ lymphoproliferative disorder, showing (a) dense, diffuse, lymphocytic infiltrate on the head and neck (×40). (b) shows pleomorphic small- to medium-sized lymphocytes (×400).

Figure 4.9 Primary cutaneous small/medium CD4+ lymphoproliferative disorder: (a) CD3+ (×40); (b) CD4+ (×40); and (c) CD8- (×40) T-cell populations.
To further aggravate pathologists, karyorrhexis and cytophagocytosis may be present in both γ/δ lymphoma and lupus panniculitis.

SPTCL is characterized by a lobular panniculitis of small- to medium-sized pleomorphic, hyperchromatic, irregularly contoured CD3+, CD4-, CD8+ T cells with an α/β phenotype that form a rim around adipocytes (Figures 4.10–4.12). Cytotoxic markers (T-cell intracellular antigen [TIA-1], granzyme-B and perforin) are often positive in the neoplastic cells; however, SPTCL is a clinically indolent disease compared with aggressive cytotoxic lymphomas such as γ/δ T-cell lymphoma. Immunohistochemical markers that help distinguish these two entities are βF-1, TCR-γ and CD56 (see Table 4.3).

<table>
<thead>
<tr>
<th>SPTCL</th>
<th>γ/δ TaCL</th>
<th>Lupus panniculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small- to medium-sized cells</td>
<td>Small- to large-sized cells</td>
<td>Small- to medium-sized cells</td>
</tr>
<tr>
<td>± Epidermotropism/dermal involvement</td>
<td>± Epidermotropism/dermal involvement</td>
<td>± Interface involvement</td>
</tr>
<tr>
<td>+ Necrosis</td>
<td>+ Necrosis</td>
<td>– Necrosis</td>
</tr>
<tr>
<td>± Plasma cells/ eosinophils</td>
<td>+ Plasma cells/ eosinophils</td>
<td>+ Plasma cells</td>
</tr>
<tr>
<td>+ Angiodestructive</td>
<td>+ Angiodestructive</td>
<td>– Angiodestructive</td>
</tr>
<tr>
<td>+ Clonality</td>
<td>+ Clonality</td>
<td>Rare clonality</td>
</tr>
<tr>
<td>CD4+/CD8+ or CD4-/CD8-</td>
<td>CD4-/CD8- (or rarely CD8+ or CD4+)</td>
<td>CD8+/ and TIA-1+/</td>
</tr>
<tr>
<td>Ki-67 elevated</td>
<td>Ki-67 elevated</td>
<td>CD123 elevated</td>
</tr>
</tbody>
</table>

γ/δ TaCL, gamma/delta T-cell lymphoma; TIA, T-cell intracellular antigen.
Clinically, SPTCL and lupus panniculitis have significant overlap as well. Work-up should include CBC, metabolic panel, anti-nuclear antibodies (ANA) and TCR PCR. Clonality is present in most cases of SPTCL, though it may be positive in lupus panniculitis. Because SPTCL is associated with systemic lupus erythematosus in some patients, and given the substantial overlap of clinicopathological findings, including clonality, some have suggested categorizing an overlap entity of ‘atypical lymphocytic lobular panniculitis’.

**Primary cutaneous γ/δ lymphoma**
As discussed above, there is histological overlap between SPTCL and primary cutaneous γ/δ lymphoma (see Table 4.3). However, the clinical
The course of primary cutaneous γ/δ lymphoma is much worse. Systemic spread to the liver, gastrointestinal tract, genitourinary system, lungs and CNS can occur, and patients commonly develop a secondary hemophagocytic syndrome, which confers an extremely poor prognosis and an urgent need for systemic chemotherapy or bone marrow transplant.

Primary cutaneous γ/δ lymphoma can show epidermal/interface, dermal and subcutaneous involvement, often within the same biopsy. These overlapping patterns may be a helpful, though not diagnostic, feature as they are extraordinarily rare in SPTCL. The infiltrates are characterized by a dense, nodular to diffuse pattern of medium- to large-sized pleomorphic cells (Figure 4.13). Rimming of the adipocytes occurs when the subcutis is involved. Immunophenotypically, the neoplastic cells are CD3+, CD4-, CD8-/+, CD56+, TCR-γ+, βF1- and EBER1- with a cytotoxic phenotype (positivity with TIA-1, granzyme-B and perforin) (Figure 4.14).6
Because of the clinically aggressive nature of γ/δ lymphoma and high association of systemic spread, complete diagnostic work-up must be performed, including a full physical examination, CBC, LDH, metabolic panel, flow cytometry, TCR PCR, HIV test, human T-cell lymphocytic virus (HTLV-1) test, full body CT or PET-CT, and lymph node and bone marrow biopsy. Monoclonality is present in almost all cases. Genetically, the γ/δ profiles differ from α/β-predominant neoplasms with overexpression of NK-cell-associated genes.7

**Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (Berti’s lymphoma)**

This cytotoxic T-cell lymphoma is characterized by marked epidermotropism of atypical CD8+ T cells (Figure 4.15). A nodular to diffuse dermal infiltrate of small- to large-sized pleomorphic T cells and immunoblasts may be present. The striking epidermotropism that
is the most prominent feature of this malignancy may be absent in the late stages of the disease (Figure 4.16). The immunophenotype is CD3+, CD4-, CD7+, CD8+, TIA-1+, CD45RA+, CD45RO-, CD56-, EBER-, βF1+ (Figure 4.17). 

The main histological differential diagnoses include CD8+ predominant MF, pagetoid reticulosis, and LyP type D. Clinical history
is needed in order to distinguish all these entities. The previously
recognized entity of generalized pagetoid reticulosis (also known
as Ketron–Goodman disease) is now better categorized as primary
Fast Facts: Diagnosing Cutaneous T-Cell Lymphoma

Cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. There can be a striking overlap with the features of primary cutaneous γ/δ lymphoma. Helpful features to distinguish primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma include lack of interface dermatitis, minimal subcutaneous involvement and an α/β rather than γ/δ phenotype.9

Monoclonal gene rearrangement is common. No recurrent genetic mutations have been identified to date, but multiple chromosomal gains and loss of 9p21 have been reported. Moreover, as with all cytotoxic lymphomas, the required work-up includes full physical examination, CBC, LDH, metabolic panel, flow cytometry, TCR PCR, HIV test, HTLV-1 test, full body CT or PET-CT and, if warranted, a lymph node and/or bone marrow biopsy.

Extranodal NK/T-cell lymphoma, nasal type

This malignancy is a cytotoxic systemic lymphoma with common cutaneous involvement. It is one of the few lymphoproliferative diseases with a known and reproducible viral cause – Epstein–Barr virus (EBV). Primary cutaneous lesions can occur without extracutaneous organ involvement; however, these patients usually develop metastatic spread to other organs over time; close monitoring is needed.

Histology shows a dense, diffuse, dermal to subcutaneous infiltrate of large, pleomorphic neoplastic cells. A mixed infiltrate of

Figure 4.17 Aggressive cytotoxic epidermotropic CD8+ T-cell lymphoma: (a) CD8+ staining in pronounced epidermotropic T cells in aggressive cytotoxic epidermotropic CD8+ T-cell lymphoma (×400). (b) Positive T-cell intracellular antigen (TIA)-1 staining consistent with a cytotoxic profile in (×400).
eosinophils, neutrophils and histiocytes may be present. Epidermotropism, interface reaction patterns, necrosis and angiodestruction may or may not be present. The immunophenotype of the neoplastic cells is CD2+, CD56+, TIA-1+. EBER1+, but CD3, CD4, CD5, CD7, CD8, CD57, βF1 and TCR-γ are routinely negative.

Molecular studies are complex; losses of TP53 and CDNK2A/p16, overexpression of MYC, MIP-1α and ABCC4, and dysregulation of JAK/STAT have been reported. The diagnostic and prognostic value of these mutations has yet to be determined.

As this is a cytotoxic lymphoma, complete systemic work-up is necessary.

**Cutaneous adult T-cell leukemia/lymphoma**

Cutaneous adult T-cell leukemia/lymphoma (ATLL) also has a known viral etiology – HTLV-1. HTLV-1 is endemic to the Caribbean islands and Japan, though should not be ruled out based solely on geographic purposes. This rare malignancy has nearly identical overlapping clinical and histological features with MF and Sézary syndrome (SS); however, repeated studies have revealed no association of the virus with MF/SS. Cutaneous findings are generally associated with indolent forms of the disease.

As stated above, the patterns seen in ATLL are identical to those seen in MF, including epidermotropism, lichenoid infiltrates and folliculotropism. Immunophenotyping reveals a T-helper profile of CD3+, CD4+, CD8- as well as a T-regulatory phenotype with FOX-P3+ expression. CD25 is also characteristically expressed in ATLL, but is not diagnostic. Monoclonality for TCR and HTLV-1 DNA is the most specific diagnostic test for distinguishing ATLL from MF/SS. Complete systemic work-up is needed as there is often leukemic and/or nodal involvement in these patients.

**Angioimmunoblastic T-cell lymphoma**

Angioimmunoblastic T-cell lymphoma (AITL) is a systemic T-cell lymphoma with common skin involvement. It is defined by effacement of nodal architecture, expansion by a polymorphous infiltrate and arborizing high endothelial venules. By definition, there must be lymph
node involvement, and diagnosis cannot be made on cutaneous findings alone. Up to 50% of patients have cutaneous involvement, which arises before AITL diagnosis in 79% of cases, concurrently in 8% and after AITL diagnosis in 13%.14

The histopathology varies with the clinical presentation. Superficial, perivascular infiltration is present in macular/papular disease (Figure 4.18), while diffuse nodular histology is associated with the clinical presentation of plaques and tumors. The neoplastic cells show a T-follicular helper cell phenotype with expression of PD-1 and CXCL-13 most specifically (Figure 4.19). In both the skin and lymph nodes, monoclonality of TCR genes is present. In the skin, B-cell clonality is rare; however, nodal immunoglobulin H rearrangements occur, especially with EBV positivity. TET2, DNMT3A, RHOA and CD28 mutations have been recognized lately, which will further our

Figure 4.18 Biopsy of a patch from a patient subsequently diagnosed with angioimmunoblastic T-cell lymphoma (×100). Insets show the perivascular lymphoplasmacytic infiltrate, a common histological finding that correlates with the clinical presentation of patches (×200 and ×400).
understanding of the etiology of this entity and improve diagnostics.\textsuperscript{15,16} As this is truly a systemic lymphoma, complete work-up is necessary, including lymph node biopsy.

**Blastic plasmacytoid dendritic cell neoplasm**

Blastic plasmacytoid dendritic cell neoplasm (BPDCN; also known as hematodermic neoplasm and blastic natural killer cell lymphoma) is characterized as a precursor hematologic neoplasm, although it may be associated with a previous myelodysplastic syndrome or rapid evolution into myeloid leukemia. It usually begins with cutaneous involvement, with subsequent leukemic spread. BPDCN is associated with a very poor prognosis. Hematology/oncology consultation and full systemic work-up should be performed rapidly upon diagnosis.

Histopathology shows a dense, diffuse, dermal and subcutaneous infiltration of medium- to large-sized neoplastic cells with plasmacytoid and blastoid morphology (Figure 4.20). Characteristically, the neoplastic cells are CD3-, CD4+, CD8-, CD56+, CD123+, TCL1+. (Figure 4.21). Given the variable staining of some markers, these stains should always be performed as a panel.
Myeloperoxidase and CD68 or CD163 are generally negative, helping to rule out leukemia cutis with or without monocytic differentiation. That being said, because variations exist in staining patterns, patients should always receive an urgent oncologic evaluation.
Figure 4.21 Blastic plasmacytoid dendritic cell neoplasm: (a) CD3- (x200); (b) CD4+ (x200); (c) CD8- (x200); (d) CD56+ (x200); and (e) CD123+ lymphocytes (x200).
Key points – pathology and diagnosis of non-mycosis fungoides CTCL

- Multiple histological variants of lymphomatoid papulosis (LyP) exist, although there is no prognostic significance between the subtypes. However, some of the subtypes histologically overlap with other forms of cutaneous T-cell lymphoma (CTCL) and clinical correlation is needed to distinguish these.

- Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is composed of sheets of CD30+ activated T cells that comprise more than 75% of the neoplastic cells. Anaplastic lymphoma kinase-1, epithelial membrane antigen and full staging work-up are used to distinguish between a primary cutaneous tumor and cutaneous involvement from nodal ALCL.

- Primary cutaneous small/medium CD4+ T cell lymphoproliferative disorder is an indolent process comprised of diffuse to nodular collections of CD4+ cells that generally present as single papules on the head and neck.

- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a subcutaneous indolent disorder composed of CD3+, CD8+, βF-1+ T cells with notable rimming of adipocytes, in contrast to γ/δ lymphoma which is clinically aggressive and comprised of dermal and subcutaneous CD4-/CD8- or rarely CD4+, CD8+ T cells with a γ/δ (TCR-γ+) phenotype.

- The clinically aggressive cytotoxic CTCLs are: primary cutaneous γ/δ lymphoma, primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (Berti’s lymphoma) and extranodal NK-T cell lymphoma, nasal type. These diseases have a CD8+ or CD56+ immunophenotype and display T-cell intracellular antigen-1+, granzyme-B+ and perforin+ cytotoxic markers. Full systemic work-up is necessary.

- Other rare secondary cutaneous T-cell processes occur from systemic T-cell lymphomas, and correlation with nodal histopathology is helpful in diagnosis.
References


Cutaneous T-cell lymphomas (CTCLs) become more frequent with increasing age and have a male predominance (male:female ratio of 2.1:1). Survival may also be worse with increasing age, which may reflect reduced innate immunity. Incidence also increases with age. Most patients with MF present with early-stage disease characterized by a long disease course but substantial morbidity (pain, pruritus, scaling), and cosmetic disfigurement may be considerable. Thirty percent of patients with MF and all those with Sézary syndrome (SS) present with advanced-stage disease, and in addition 25% with early MF will progress to advanced disease.

Staging alongside identification of the good/poor prognostic factors will enable more aggressive subtypes that require more aggressive medical intervention to be identified and treated appropriately.

The revised TNMB staging system
The Mycosis Fungoides Cooperative Group staging system was developed in the 1970s and was the preferred staging system for over 25 years. It provided prognostic information, but there were inconsistencies; for example, median survival in stage IIB was worse than that for stage III, and patients with folliculotropic patch/plaque (stage IB) MF had a worse prognosis than those with tumor-stage disease (stage IIB).

A revised system (Table 5.1) was proposed by the International Society for Cutaneous Lymphoma (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization for the Research and Treatment of Cancer (EORTC). This revised staging introduced a blood classification (B0–2) alongside the conventional tumor–node–metastasis (TNM) categories. The TNMB system uses tumor (T1–4), nodal (N0–3), metastasis (M0–1) and blood (B0–2) classification to produce nine stages from IA–IVB and provides prognostic information (see Table 5.1). Stages IA–IIA are considered early-stage disease and IIB–IVB advanced stage.
TABLE 5.1
ISCL/EORTC staging system for cutaneous T-cell lymphoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Node (N)</th>
<th>Metastasis (M)</th>
<th>Blood (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IIA</td>
<td>1, 2</td>
<td>1, 2</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IIB</td>
<td>3</td>
<td>0–2</td>
<td>0</td>
<td>0, 1</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
<td>0–2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
<td>0–2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IVA</td>
<td>1–4</td>
<td>0–2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>IVA 1</td>
<td>1–4</td>
<td>3</td>
<td>0</td>
<td>0–2</td>
</tr>
<tr>
<td>IVA 2</td>
<td>1–4</td>
<td>0–3</td>
<td>1</td>
<td>0–2</td>
</tr>
</tbody>
</table>

**T1**: patches/plaques <10% body surface area; **T1a**: patch only; **T1b**: patch and plaque.

**T2**: patches/plaques >10% body surface area; **T2a**: patch only; **T2b**: patch and plaque.

**T3**: Tumors > 1 cm in diameter; **T4**: Erythroderma ≥ 80% body surface area.

**N0**: No clinically palpable lymph nodes (LN) (nodes all < 15 mm); **N1**: Clinically palpable peripheral LN with dermatopathic histopathology or scattered atypical cells; **N1a**: clone negative; **N1b**: clone positive; **N2**: Clinically palpable peripheral LN with histopathological evidence of lymphomatous infiltration; **N2a**: clone negative; **N2b**: clone positive; **N3**: Clinically palpable peripheral LN with complete effacement of the nodal architecture; **Nx**: Clinically palpable peripheral LN (nodes > 15 mm) with no histology.

**B0**: No significant blood involvement (< 5% atypical cells of peripheral blood lymphocytes [PBL]); **B0a**: clone negative; **B0b**: clone positive; **B1**: low blood tumor burden > 5% of PBL are atypical (Sézary) cells, but does not meet criteria for B2; **B1a**: clone negative; **B1b**: clone positive; **B2**: high blood tumor burden > 1000 μ/L of atypical (Sézary) lymphocytes with positive clone.

**M0**: no visceral disease; **M1**: visceral disease (confirmed histologically unless splenomegaly).

Patients with early-stage disease tend to have a favorable prognosis of more than a decade and are managed with skin-directed therapy or a ‘wait and see’/‘expectant’ approach. Patients with late-stage disease tend to have an aggressive clinical course and typically need systemic therapy.

Cutaneous lymphomas other than MF/SS are classified separately using a TNM system; however, this staging system has not been validated prospectively for prognosis.

‘Skin scoring’. The current T class does not reflect the skin tumor burden. A crude distinction between stage T1 and T2 disease is dependent on involvement of more than 10% of body surface area, while T4 is defined as more than 80% involvement. In T3 there is no minimum body surface area involvement and the presence of one tumor of more than 1 cm diameter defines disease. Use of the modified severity weighted assessment tool (mSWAT) provides additional information to staging in MF/SS. The mSWAT calculates the amount of body surface area covered by each type of MF/SS lesion (patch, plaque, tumor) in each of 12 areas of the body (head, neck, anterior trunk, arms, forearms, hands, posterior trunk, buttocks, thighs, legs, feet, groin), and then applies a weighting factor (×1, plaque ×2, tumor ×4) to produce a numerical value out of a total of 400.8

While there are always problems with any type of scoring system, the mSWAT score allows disease tumor burden to be accurately recorded to assess responses to treatment, and is useful in clinical trials.

Prognosis
Patient survival according to stage of disease was reported in a recent London cohort of more than 1500 patients.2 Early-stage disease (IA–IIA) had a long median survival of 16–35 years and 5-year disease-specific survival (DSS) of 89–98% (Table 5.2). Signs in early-stage disease that indicated a better prognosis in this and other studies included presenting at a young age, poikiloderma, hypopigmentation and the association of lymphomatoid papulosis (LyP). Signs associated
with a worse prognosis included male sex, plaques, folliculotropism and enlarged lymph nodes.

A large international multicenter study of 1275 patients with advanced-stage MF/SS reported survival of 63 months, with 2- and 5-year survival rates of 77% and 52%, respectively. The median overall survival for patients with stage IIB disease was 68 months; patients diagnosed with stage III disease had slightly better survival than patients with stage IIB disease, although patients diagnosed with stage IV disease had significantly worse survival (48 months for stage IVA and 33 months for stage IVB).

This study tested ten candidate prognostic markers (stage, age, sex, cutaneous histological features of folliculotropism, CD30 positivity, proliferation index, large cell transformation, white blood cell/lymphocyte count, serum lactate dehydrogenase, and presence of identical T-cell clone in blood and skin) with the aim of developing a prognostic index that would identify advanced-stage patients at risk of progression. Each parameter was recorded at diagnosis and tested against overall survival. Four independent prognostic markers were found for worse survival: stage IV disease, age greater than 60 years, large cell transformation and increased LDH. Combining these four
factors in a prognostic index model identified the following three risk
groups across stages with significantly different 5-year survival rates:
low risk (68%), intermediate risk (44%) and high risk (28%). This
prognostic model may be used to stratify patients with advanced-stage
disease who require more aggressive treatments.

Key points – staging and prognosis

- Mycosis fungoides (MF) can be categorized according to nine
  stages, from IA to IVB.
- Stages IA–IIA are considered early-stage disease and have
  a good prognosis, while stages IIB–IVB are advanced stage
disease and progress rapidly.
- Early-stage lesions of the skin include patches and plaques.
- Advanced-stage skin lesions include tumors and erythroderma.
- Some patients with early-stage disease will have near-normal
  life expectancy, while advanced-stage survival is 1–4 years.
- Poor prognostic indicators for survival in MF include increasing
  age, raised lactate dehydrogenase, lymph node involvement
  and large cell transformation in the skin.
References


Useful resources

UK
Bloodwise
Tel: +44 (0)20 7504 2200
www.bloodwise.org.uk

Cutaneous Lymphoma Group
www.kcl.ac.uk/lsm/research/divisions/gmm/departments/dermatology/Groups/
WhittakerLab/index.aspx

Lymphoma Association
Helpline: 0808 808 5555
enquiries@lymphomas.org.uk
www.lymphomas.org.uk

USA
The American Society of Dermatopathology
Tel: +1 847 686 2231
www.asdp.org

Cutaneous Lymphoma Foundation
Tel: +1 248 644 9014
www.clfoundation.org

The Leukemia & Lymphoma Society
Toll-free: 1 800 955 4572
infocenter@lls.org
www.lls.org

Lymphoma Research Foundation
Helpline: 1 800 500 9976
Tel: +1 212 349 2910
helpline@lymphoma.org
www.lymphoma.org

United States and Canadian Academy of Pathology
Tel: +1 706 733 7550
help@uscap.org
www.uscap.org

United States Cutaneous Lymphoma Consortium
Tel: +1 770 613 0932
www.usclc.org

International
EORTC Cutaneous Lymphoma Taskforce
www.eortc.org/research-groups/cutaneous-lymphoma-task-force

International Academy of Pathology
www.iapcentral.org

International Society for Cutaneous Lymphomas
www.cutaneouslymphoma.org
Useful resources

International Society of Dermatopathology
Tel: +1 650 726 5481
www.intsocdermpath.org

Leukaemia & Blood Cancer NZ
Toll-free: 0800 15 10 15
Tel: +64 (0)9 638 3556
info@leukaemia.org.nz
www.leukaemia.org.nz

Leukaemia Foundation (Australia)
Toll-free: 1 800 620 420
Tel: +61 (0)7 3866 4000
info@leukaemia.org.au
www.leukaemia.org.au

Leukemia & Lymphoma Society of Canada
Tel: +1 877 668 8326
AdminCanada@lls.org
www.llscanada.org

Lymphoma Australia
Tel: +61 (0)431 483 204 or 1 800 359 081
enquiries@lymphoma.org.au
www.lymphoma.org.au

Lymphoma Foundation Canada
Toll-free: +1 866 659 5556
Tel: +1 905 858 5967
info@lymphoma.ca
www.lymphoma.ca

Useful websites
Focus on chronic lymphocytic leukemia
www.focusoncll.org
Focus on mantle cell lymphoma
www.focusonmcl.org
Lymphoma Information Network
www.lymphomainfo.net

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ALCL 65
ATLL 75
BPDCN 77–8
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small/medium CD4+ 66
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