Cutaneous T-cell lymphoma

Primary cutaneous T-cell lymphomas include a wide variety of lymphoproliferative disorders with disease confined to the skin at the time of presentation. This article reviews this heterogeneous condition focusing mainly on mycosis fungoides, Sezary syndrome and primary cutaneous CD30-positive lymphoproliferative disorders.

The term primary cutaneous lymphomas refers to cutaneous T-cell lymphomas (CTCL) and cutaneous B-cell lymphomas (CBCL) that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. The skin represents the second most common location for extranodal non-Hodgkin's lymphomas after the gastrointestinal tract, with an estimated annual incidence of 1/100 000 (Groves et al, 2000).

Recent advances in molecular techniques, including immunophenotyping and gene rearrangement studies to determine clonality, have led to more consistent subclassifications that take into account not only histological features but also clinical and immunophenotypic criteria. Classifications based on histological criteria, such as the Kiel classification, the Working formulation and the revised European American classification, have been superseded by the recent World Health Organization–European Organization for the Treatment of Cancer (WHO-EORTC) (Willemze et al, 2005) (*Table 1*). This is of major importance as primary cutaneous lymphomas often have a completely different clinical behaviour and prognosis from histologically similar systemic lymphomas, which may involve the skin secondarily, and therefore require different types of treatment.

Mycosis fungoides (MF), Sezary syndrome (SS), lymphomatoid papulosis (LyP) and primary cutaneous CD30+ anaplastic large cell lymphoma (PCALCL) constitute more than 90% of primary CTCLs (Willemze et al, 2005). According to Willemze et al (2005), authors of the WHO-EORTC, the classification of the remaining rare group of CTCL remains difficult and confusing. With few exceptions, these tumours behave aggressively and require, in most cases, systemic chemotherapy (Willemze et al, 2005).

Table 1. World Health Organization-European Organization for the Treatment of Cancer classification of cutaneous T-cell lymphomas and natural killer (NK)-cell lymphomas

Mycosis fungoides	
Mycosis fungoides variants and subtypes	Folliculotropic disease
	Pagetoid reticulosis
	Granulomatous slack skin
Sezary syndrome	
Adult T-cell leukaemia/lymphoma	
Primary cutaneous CD30+ lymphoproliferative disorders	Primary cutaneous anaplastic large cell lymphomas
	Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma	
Extranodal NK/T-cell lymphoma, nasal type	
Primary cutaneous peripheral T-cell lymphoma, unspecified	Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
	Cutaneous g/d T-cell lymphoma (provisional)
	Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)

From Willemze et al (2005)

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Aetiology and pathogenesis

Aetiology

The aetiology of these disorders remains elusive. For over 20 years one of the theories associated with the development of MF has been that this is a disease of antigen persistence associated with chronic lymphocytic stimulation and eventual transformation of benign lymphocytes to a low-grade malignant lymphoma (Girardi et al, 2004).

A putative role for infectious agents or occupational exposure has been excluded. Whereas viruses have been identified as aetiological agents in at least two lymphomas that may involve the skin (human T-cell lymphotrophic virus (HTLV)-associated adult T-cell lymphoma-leukaemia and Epstein–Barr virus-associated extranodal nasal type natural-killer-T-cell lymphoma) no such relationship has been confirmed for MF (Girardi et al, 2004).

Pathophysiology

Considerable progress has been made in the understanding of the pathogenesis of CTCL with the application of novel molecular techniques. Girardi et al (2004) highlight a number of key events in the pathogenesis of CTCL, particularly in MF. These include the unifying propensity of these lymphomas to home to the skin, to function in an activated state escaping normal apoptotic mechanisms, and to achieve clonal dominance (Girardi et al, 2004).

Skin homing

As subsets of T cells are thought to circulate through the mucosal structures (mucosa-associated lymphoid tissue) it has been suggested that there is a similar subset of T lymphocytes trafficking through the skin (skin-associated lymphoid tissue). The identification of a receptor for a subset of skin associated circulating T cells (cutaneous lymphocyte-associated antigen (CLA) which is defined by its reactivity with a monoclonal antibody, endothelial cell antigen (HECA-452) by Picker et al (1990) supports this concept. Circulating lymphoma cells expressing CLA migrate to the skin through the interaction between CLA and E-selectin, expressed in endothelial cells. This occurs in response to chemokines emanating from the epidermis (e.g. chemokine ligand 17 (CCL17) which interacts with the chemokine receptor 4 (CCR4) expressed by T cells). Indeed tumour cells in patch-plaque stage MF express CLA and CCR4 and high levels of expression of CCL17 in the skin lesions (Girardi et al, 2004).

Persistent T-cell activation

Malignant cells in patients with MF frequently express several activation markers such as CD45RO, proliferating-cellular antigen, and the interleukin-2a (IL-2a) receptor (CD25). After stimulation of the IL-2 receptor, activated T cells undergo phosphorylation of several intracellular proteins in the janus kinase activity-signal transducers and activators of transcription proteins (JAK-STAT) signalling pathway. Constitutive activation of STAT3 occurs in MF, which could contribute to a persistent state of activation of malignant T cells (Girardi et al, 2004). However, evidence that a truncated STAT5 protein is expressed in SS suggests that the IL-2 signalling pathway is dysregulated with a possible failure of T-cell activation induced cell death (Mitchell et al, 2003). This may also contribute to the marked T-cell anergy that these tumour cells exhibit.

Clonal dominance

Specific chromosomal abnormalities have been found in numerous leukaemias and lymphomas. These chromosomal translocations result in clonal expansion through a direct effect such as amplification of oncogenes leading to over-expression or inactivation of tumour suppressor genes (Cerroni et al, 1994; Deininger et al, 2000). Although such molecular signatures have not yet been identified in CTCL, mutations in the cell-cycle/apoptosis regulator p53 are associated with disease progression in MF (Lauritzen et al, 1995; McGregor et al, 1995, 1999; Marrogi et al, 1999; Girardi et al, 2004) and inactivation of P15/P16 genes through promoter hypermethylation have also been described frequently (Navas et al, 2000; Scarisbrick et al, 2002). In addition a high rate of chromosomal instability and microsatellite instability have been detected (Scarisbrick et al, 2000, 2003).

Physiological activation of T cells is followed by activation-induced cell death to prevent excessive cellular accumulation. This is partly mediated by interaction of cell-surface Fas (CD95) and Fas ligand. Cytotoxic lymphocytes also utilize this mechanism to mediate their antitumour effect by expression of Fas ligand and the engagement of Fas on the malignant cells. This mechanism is evaded in MF as the disease progresses through a decrease in Fas expression, either as a result of mutations, 10q allelic loss or promoter hypermethylation, leading to gene inactivation and a non-functioning Fas protein (Zoi-Toli et al, 2000; Dereure et al, 2002). Expression of Fas ligand by tumoural cells themselves may also eliminate potential antitumour CD8 T cells (Girardi et al, 2004).

Initial assessment of CTCLs

The following recommendations are based on guidelines for the management of primary cutaneous T-cell lymphomas by Whittaker et al (2003):

- Repeated skin biopsies are often required to confirm the diagnosis of CTCL. Histology, immunophenotypic studies and preferably T-cell receptor gene rearrangement studies should be performed on all tissue samples
- All patients (with exception of early stages of MF and LyP) should be reviewed by an appropriate multidisciplinary team (dermatologists, clinical or medical oncologist or haematologist and a dermatopathologists) for confirmation of diagnosis and to establish a management strategy
- Initial staging computed tomography (CT) scans are required for all patients (except in early stages of MF and LyP)
- At diagnosis peripheral blood samples should be analysed for total white count, lymphocyte and Sezary cell counts, serum lactate dehydrogenase (LDH), liver and renal function, lymphocyte subsets, CD4/CD8 ratios, HTLV-1 serology and, preferably, T-cell receptor gene rearrangement studies
- Bone marrow aspirate or trephine biopsies are required for CTCL variants (except for LyP) and late stages of MF (stage IIB or above (*Table 2*)).

Mycosis fungoides

MF is the most common type of CTCL and accounts for almost 50% of all primary cutaneous lymphomas (Willemze et al, 2005).

Clinical features

MF typically affects older adults (median age at diagnosis is 55–60 years, and the male to female ratio is 1.6–2.0:1) but may occur in children and adolescents. It has an indolent course with slow progression over years and sometimes decades from patches to more infiltrated plaques that are polymorphic in colour and shape. In a minority of patients it eventually progresses to tumours. Lymph nodes and visceral organs may be involved in the

later stages of the disease. There is a predilection for the buttocks and other sun-protected areas and skin lesions are usually not pruritic. Patients with tumour stage MF often show a combination of patches, plaques and tumours, which often show ulceration. If only tumours are present, and there is no history of patches or plaques, another variant of CTCL should be considered (Willemze et al, 2005). Bullous, hyper- and hypopigmented variants have been described and these exhibit similar clinical behaviour to classical MF. Folliculotropic MF, pagetoid reticulosis and granulomatous slack skin are now considered as variants of MF under the new WHO-EORTC classification (Willemze et al, 2005).

Histopathology

Patch stage

Superficial band-like or lichenoid infiltrate made of lymphocytes and histiocytes. The characteristic atypical lymphocytes with 'cerebriform' nuclei are often scanty and confined to the epidermis (epidermotropism).

Plaques

Epidermotropism more evident often with colonization of the basal layer. Intraepidermal collections of atypical cells form Pautrier's microabcesses that are pathognomonic but observed only in a minority of cases.

Tumour stage

Dermal infiltrate is more evident, and epidermotropism may be lost. The degree of cellular atypia becomes more marked and the tumour cells increase in number and size. Transformation to a large cell morphology, either CD30+ or CD30-, may occur and can be associated with a bad prognosis (Willemze et al, 2005).

Table 2. Clinical staging system for cutaneous T-cell lymphoma

TNM classification	T1: Patches or plaques ≤10% of the body surface area
	T2: Patches or plaques ≥10% body surface area
	T3: Tumours
	T4: Erythroderma
	N0: No palpable nodes
	N1: Palpable nodes without histological involvement (dermopathic)
	N2: Non-palpable nodes with histological involvement
	N3: Palpable nodes with histological involvement
	M0: No visceral disease
	M1: Visceral disease
	B0: No haematological involvement
Bunn and Lambert system	Stage IA: T1 N0
	Stage IB: T2 N0
	Stage IIA: T1/2 N1
	Stage IIB; T3 N0/1
	Stage III: T4 N0/1
	Stage IVA: T-any N2/N3
	Stage IVB: T-any N-any M1

*Peripheral blood involvement is not addressed in these classifications. From Whittaker et al (2003)

Immunophenotype

The cells in MF have a mature CD3+, CD4+, CD45RO+, CD7-, CD8- memory T-cell phenotype. Demonstration of an aberrant phenotype (loss of pan T-cell markers such as CD2, CD3 and CD5) is often seen and can be helpful in the diagnosis (Willemze et al, 2005).

Genetic studies

No disease-specific translocations have been identified in MF, however, chromosomal loss at 10q (Karenko et al, 1999; Scarisbrick et al, 2001a; Mao et al, 2003) and inactivation of p15, p16 and p53 tumour suppressor genes are commonly seen (McGregor et al, 1995; McGregor et al, 1999; Marrogi et al, 1999; Navas et al 2000; Scarisbrick et al 2002, Lauritzen et al, 2005). Microsatellite instability is present and appears to be a result of hypermethylation of mismatch repair genes (Scarisbrick et al, 2000, 2003). Amplification of JunB is present in more advanced disease (Mao et al, 2003). A clonal pattern of T-cell receptor gene rearrangements are detected in most cases (Bottaro et al, 1994; Theodorou et al, 1995; Willemze et al, 2005).

Prognosis

The most important prognostic factor is dependent on stage and, in particular, on the extent and type of skin lesions and the presence of extracutaneous disease (*Table 3*). Patients with limited patch or plaque stage MF have a similar life expectancy to an age-, sex-, and race-matched control population. Patients with effaced lymph nodes, visceral involvement, and large cell transformation can expect an aggressive clinical course. Patients usually die of infections or systemic involvement (Siegel et al, 2000; Willemze et al, 2005). The presence of a peripheral blood T-cell clone may indicate which patients with early stage disease are likely to develop disease progression (Fraser-Andrews et al, 2000).

Therapy

Skin-targeted therapies such as ultraviolet β/psoralen and ultraviolet α (PUVA), topical application of nitrogen mustard or carmustine (BCNU) or radiotherapy, including total skin electron beam irradiation, are preferred when the disease is confined to the skin. In patients with limited patch stage disease, topical steroids or bexarotene gel (new retinoid) can be used (Siegel et al, 2000; Whittaker et al, 2003; Willemze et al, 2005). Biological agents such as interferon alpha (+/- PUVA) and other cytokines (e.g. IL-12), bexarotene, and CD25 receptor targeted cytotoxic proteins (e.g. DAB389 IL-2, Denileukin difitox, a recombinant fusion protein of diphtheria toxin and IL-2) are increasingly used in MF.

Multiagent chemotherapy is used when there is unequivocal lymph node or visceral involvement or in tumour stage disease when skin-targeted therapy has failed.

Sezary syndrome

Classically SS is defined by the triad of erythroderma, lymphadenopathy and presence of Sezary cells in peripheral blood. Vonderheid et al (2002) recommended the following criteria for the diagnosis of SS:

- An absolute Sezary cell count of at least 1000 cells per mm^3
- Demonstration of immunophenotypical abnormalities: expanded CD4+ T-cell population resulting in a CD4/CD8 ratio of more than 10 or/and loss of any or all pan T-cell antigens (e.g. CD2, CD3 and CD5)
- Presence of a T-cell clone by molecular or cytogenetic methods in peripheral blood.

The combination of the presence of a T-cell clone and one of the above cytomorphological and immunophenotypical criteria is necessary to distinguish SS from other inflammatory dermatoses that cause erythroderma (e.g. psoriasis, eczema, or ptyriasis rubra pilaris).

Clinical features

SS is a rare disease that occurs exclusively in adults. It is characterized by erythroderma, which may be associated with marked exfoliation, oedema and lichenification. It is intensely pruritic. Lymphadenopathy, alopecia, onychodystrophy, and palmoplantar hyperkeratosis are common findings (Siegel et al, 2000; Willemze et al, 2005).

Histopathology

The histological features of SS in skin are similar to those in MF. However, the cellular infiltrate may be non-diagnostic in 30% of cases and epidermotropism may be absent (Trotter et al, 1997). Involvement of lymph nodes is characterized by partial or total effacement of the normal architecture of the lymph nodes, although some patients only exhibit dermatopathic features. The bone marrow may also be affected with infiltration being sparse and often interstitial (Willemze et al, 2005).

Immunophenotype

The neoplastic T-cells usually have a CD3+, CD4+, CD8- phenotype and Sezary cells in peripheral blood often show loss of CD7 and CD26 (Willemze et al, 2005).

Genetic features

T-cell receptor genes are clonally rearranged and the detection of a clone in peripheral blood is invaluable to distinguish SS from benign forms of erythroderma. Specific translocations for SS have not been identified in SS but complex karyotypes are common. Chromosomal amplification of JunB, a member of the AP-1 transcription factor complex involved in cell proliferation, and Th2 cytokine expression by T cells, have been identified in SS (Mao et al, 2003; Willemze et al, 2005).

Prognosis

The prognosis is often poor, with a median survival of 2–4 years. Most patients die of opportunistic infections that are the result of immunosuppression. The presence of nodal involvement is a poor prognostic feature (Scarisbrick et al, 2001b).

Therapy

Extracorporeal photopheresis, either alone or in combination with other treatment modalities (e.g. interferon-α), has been reported as an effective treatment in SS and erythrodermic MF (Edelson et al, 1987; Russell-Jones, 2000). This therapy involves a form of leukapheresis with psoralen added to a buffy-coat enriched peripheral blood fraction, which is then exposed to UVA. The irradiated cells are then returned to the patient. The UVA irradiated cells undergo apoptosis and there is emerging evidence that the reinfused cells stimulate an immune response against the malignant cells (Siegel et al, 2000). The reported overall response rates vary from 30–80% with complete responses of 14–25%. This is probably dependent on both the CD8 count and the total Sezary cell count in peripheral blood (Whittaker et al, 2003).

Other alternatives include the use of single agent palliative chemotherapy (chlorambucil, deoxycoformycin or methotrexate), interferon-α and PUVA or new therapies such as bexarotene or alemtuzumab (anti-CD52) Siegel et al, 2000; Whittaker et al, 2003; Willemze et al, 2005).

CD30+ lymphoproliferative disorders

Primary cutaneous CD30+ lymphoproliferative disorders represent the second most common group of CTCL, accounting for 30% of all CTCL. This group includes PCALCL, LyP and borderline cases. It is now generally accepted that LyP and PCALCL form a spectrum of the same disease and histological criteria alone are often insufficient to distinguish between these entities. The clinical appearance and course need to be correlated with the histopathology for a definite diagnosis and correct treatment of these conditions. This is particularly important for patients with borderline cases in which, despite clinical correlation, a definite distinction between LyP and PCALCL cannot be made (Liu et al, 2003; Willemze et al, 2005).

Table 3. Prognosis in mycosis fungoides

Extent of disease	% disease-specific survival 10 years after diagnosis
Limited patch/plaque stage disease (IA)	≥95%
Generalized patch/plaque stage disease (IB)	≥80%
Tumour stage (IIB)	≤50%
Histologically documented lymph node involvement (IVA)	≤25%

Lymphomatoid papulosis

Definition and clinical features

LyP is a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease that tends to occur mostly in middle-aged adults. It affects the trunk and extremities and skin lesions appear in crops and may heal to leave varioliform superficial scars. The duration of the disease may vary from several months to more than 40 years. In up to 20% of patients, LyP may be preceded, associated with or followed by other CTCL (e.g. MF or PCALCL) or Hodgkin's lymphoma (Liu et al, 2003; Willemze et al, 2005).

Histopathology and genetic studies

Histopathologically three types of LyP are distinguished:

- LyP type A: clusters of Reed Sternberg-like CD30+ cells intermingled with numerous inflammatory cells
- LyP type B (uncommon <10%): epidermotropic infiltrate of small atypical cells with cerebriform nuclei similar to those observed in MF. The cells do not express CD30
- LyP type C: clusters of large anaplastic CD30+ cells with a very sparse inflammatory cell infiltrate.

Most cases show a mixed type A/B pattern. T-cell rearrangement studies demonstrate the presence of a clonal population in 60–70% of cases (Liu et al, 2003; Willemze et al, 2005).

Prognosis

LyP has an excellent prognosis. Bekkenk et al (2000) reported a series of 118 patients with LyP followed for a median of 77 months; only five patients (4%) developed a definite systemic lymphoma and only two (2%) died of systemic disease. The prognostic factors for the development of a systemic lymphoma are unknown.

Treatment

No curative therapy is available at present and the potential short-term benefits of treatment should be balanced carefully against the potential side effects. Low-dose methotrexate is probably the most effective treatment but often patients relapse shortly after discontinuation of therapy. Other options include PUVA and topical chemotherapy (Bekkenk et al, 2000; Liu et al, 2003; Willemze et al, 2005).

PCALCL

Definition and clinical features

PCALCL is composed of large cells that express CD30. Most patients are adults that present with solitary or localized nodules and tumours, and sometimes papules, which often show ulceration. Multifocal lesions appear in 20% of patients. The lesions may occasionally show partial or total spontaneous regression. Extracutaneous dissemination may occur in 10% of patients and mainly involves local lymph nodes (Bekkenk et al, 2000; Liu et al, 2003; Willemze et al, 2005).

Histopathology, immunophenotype and genetic studies

There is a diffuse, non-epidermotropic infiltrate with cohesive sheets of large CD30+ cells that are most commonly anaplastic but may be pleomorphic or immunoblastic. The cells show an activated CD4+ phenotype and, unlike systemic CD30+ anaplastic large cell lymphoma (ALCL), express CLA but do not express epithelial membrane antigen and are anaplastic lymphoma kinase (ALK) negative. Expression of ALK is indicative of the t(2;5) chromosomal translocation. This is important, as systemic ALCL has a significantly worse prognosis and often requires chemotherapy whereas PCALCL has an excellent prognosis and chemotherapy is only required when there is evidence of secondary systemic involvement. Most cases show clonal T-cell gene rearrangements (Bekkenk et al, 2000; Liu et al, 2003; Willemze et al, 2005).

Prognosis

The prognosis is excellent with a 10-year disease-related survival exceeding 90%. Patients presenting with multiple skin lesions or involvement of local regional lymph nodes have similar prognosis to those with solitary skin lesions (Bekkenk et al, 2000; Liu et al, 2003; Willemze et al, 2005).

Treatment

Radiotherapy or surgical excision is the treatment of choice for solitary lesions. For multifocal disease the choices include radiotherapy or low dose methotrexate. Chemotherapy is only indicated if there is evidence of systemic involvement (Bekkenk et al, 2000; Liu et al, 2003; Willemze et al, 2005). BJHM

Conflict of interest: none.

KEY POINTS

- Classification of primary cutaneous T-cell lymphomas (CTCL) must be based not only on histopathological criteria but also on immunophenotypic, genetic and, more importantly, clinical features.
- Clinicopathological correlation is crucial for an appropriate diagnosis and formulation of a management strategy, which should be done by a multidisciplinary team.
- Recent advances in molecular techniques have provided unique insights into the pathogenesis of CTCL and have contributed to a better classification as well as forming the basis for new emerging therapies.
- The skin is the second most common location for extranodal non-Hodgkin's lymphoma.
- Mycosis fungoides is the most common primary CTCL and patients with early stage disease have a similar survival to the general population. Clinical staging is the most important prognostic factor.
- Lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma represent a spectrum of the same disease and correlation of histopathological features with clinical features is often necessary to distinguish between the two.

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