Mycosis fungoides and Sézary syndrome

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Mycosis fungoides and Sézary syndrome are the most common of the cutaneous T-cell lymphomas, which are a heterogeneous group of neoplasms that affect the skin as a primary site. Although the aetiologies of mycosis fungoides and Sézary syndrome are unknown, important insights have been gained in the immunological and genetic perturbations that are associated with these diseases. Unlike some B-cell lymphomas, cutaneous T-cell lymphomas as a group are rarely if ever curable and hence need chronic-disease management. New approaches to treatments are being investigated and include biological and cytotoxic drugs, phototherapy, and monoclonal antibodies that are directed towards novel molecular targets. New molecular technologies such as complementary-DNA microarray have the potential to increase the accuracy of diagnosis and provide important prognostic information. Treatments can be combined to greatly improve clinical outcome without substantially increasing toxic effects in advanced disease that is otherwise difficult to treat. Although present treatment strategies are generally not curative, there is hope that experimental treatments, particularly immunotherapy, might eventually reverse or suppress the abnormalities of mycosis fungoides and Sézary syndrome to the point at which they become non-life-threatening, chronic diseases.

Lancet 2008; 371: 945–57

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Introduction

The French physician Jean Louis Alibert published the first description of mushroom-like skin tumours in a patient with mycosis fungoides nearly 200 years ago.[2] Since then, this disease has been of interest to clinicians because of the unique skin tropism that malignant T cells show. Sézary syndrome was recognised in 1938 and is a T-cell lymphoma of the skin and peripheral blood. In 1975, Edelson and Lutzner[3] first coined the term cutaneous T-cell lymphoma (CTCL), which initially referred to mycosis fungoides and Sézary syndrome—the two most common forms of this group. The CTCLs are now known to encompass a broad group of cutaneous lymphomas, including primary cutaneous anaplastic large-cell lymphoma and other rare diseases (panel 1), which vary in histology, immunophenotype, and prognosis.[4–6] Several reviews detail the clinical features and therapy of these rare CTCLs.[1,2,7]

Recent classification systems have drawn attention to the biological importance of clinical features, in addition to tumour morphology, and have integrated them into the pathological definition of lymphomas.[1,2,5] After consensus meetings in 2002 and 2003, the most useful features of the WHO classification of lymphoid malignancies[4] and the European Organisation for Research and Treatment of Cancer (EORTC) classification of cutaneous lymphomas[8] were incorporated into a single classification scheme (WHO-EORTC).[1] Although Sézary syndrome was previously often classified as a variant of mycosis fungoides, the WHO-EORTC classification lists these two diseases as separate entities with distinctive clinical features (panel 1).[1] This Seminar will focus on advances in the diagnosis, pathogenesis, and treatment of these two disorders.

Epidemiology

According to a recent analysis of data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results, the overall age-adjusted incidence of CTCLs (including rare entities described in panel 1) every year from 1973 to 2002 was 6·4 cases per million.[9] The incidence of CTCLs has continued to increase over the past three decades by 2·9 cases per million per decade, which could be a result of better diagnosis since regional incidence is highly correlated to high physician density and socioeconomic status.[9] Mycosis fungoides accounted for 72% of CTCL cases reported from 1973 to 2002, whereas Sézary syndrome accounted for 2·5%.[9,10] The incidence of CTCL was roughly 50% greater in black people than in white people.[9] Men are affected twice as often as are women, and incidence increases greatly with age. Childhood cases of mycosis fungoides, however, have been reported.[9–11]

Genetics

Changes in a number of tumour suppressor and apoptosis-related genes (table 1) have been recorded in patients with mycosis fungoides and Sézary syndrome, although how most of these alterations affect T-cell behaviour is still not clear. In 50–85% of patients with these disorders who were tested, one frequent genetic abnormality seems to interfere with expression of NAV3, which might act as a tumour suppressor in T cells.[12] Mutations in the p53, p15, p16, JunB, and *PTEN* genes generally occur in later-stage disease, suggesting that they are secondary genetic events and not part of disease

Search strategy and selection criteria

Information in this Seminar was obtained through Medline searches of mycosis fungoides, Sézary syndrome, and skin lymphoma over the past 5 years, with key words "diagnosis", "pathology", "pathogenesis", and "treatment". The WHO-European Organisation for Research and Treatment of Cancer classification was used for reference and as an organisational guide.[1] Recent advances presented at scientific meetings and available as abstracts on meeting websites were also included. Only references published in English were included.

***Panel 1:* Classification of cutaneous T-cell lymphomas by WHO and the European Organisation for Research and Treatment of Cancer[1]**

Indolent clinical behaviour

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

Aggressive clinical behaviour

- Sézary syndrome
- Primary cutaneous natural-killer/T-cell lymphoma, nasal-type
- Primary cutaneous aggressive CD8+ T-cell lymphoma*
- Primary cutaneous gamma/delta (γ/δ) T-cell lymphoma*
- Primary cutaneous peripheral T-cell lymphoma, unspecified

*Provisional entities.

	Percentage affected
p16 (INK4a)	18–73%
p15 (INK4b)	5–27%
p14 (ARF)	0–18%
PTEN	10–45%
p53	0–66%
JunB	50–91%
HLA-G	0–28%
Fas	14–59%
Fas ligand	50–83%
Nav3	50–85%

Table 1: **Molecular changes associated with mycosis fungoides and Sézary syndrome by genetic lesion[12–16]**

initiation (table 1).[13–17] Loss of normal apoptotic T-cell pathways, including Fas expression, has also been reported.[18,19]

Complementary DNA (cDNA)-based microarray analysis holds great promise in identification of mechanisms of pathobiology and new therapeutic targets in mycosis fungoides and Sézary syndrome, though its application is confounded by the scarcity of malignant cells compared with healthy cells in biopsy samples of skin.[20] Ten genes have been identified as being associated with signalling through the tumour necrosis factor receptor and anti-apoptotic activity, suggesting that these pathways might promote malignant T-cell growth.[21] Furthermore, expression analysis of only five genes can be used to diagnose Sézary syndrome with great accuracy, despite highly variable (5–99% of circulating lymphocytes) peripheral blood involvement;[22] analysis of ten genes can identify patients with especially poor prognosis independently of tumour burden.[23] Although microarray analysis is not feasible in most commercial diagnostic laboratories, real-time PCR methods that are less complex can lead to improved diagnostic accuracy or prognosis, or both.

Clinical features

Mycosis fungoides presents in the skin with erythematous patches, plaques, and less frequently, tumours (figure 1). Scaling is often found on patch and plaque lesions, although generally not to the degree that is seen in patients with psoriasis. Rarely, lesions are atrophic and dyspigmented in a variant termed poikilodermatous mycosis fungoides. A patient with mycosis fungoides typically has many lesions of long-standing duration, typically months to years, which are usually located in areas infrequently exposed to sunlight (figure 1). Lesions are less commonly located on the face except in tumour-stage disease (figure 1) or with folliculotropic variants of this disease.[24] By comparison, psoriasis—a benign inflammatory skin disorder—also presents with symmetric, erythematous plaques but usually has less variability in lesions, more intense erythema of individual lesions, and a more general distribution, with a predeliction for the elbows and knees, than does mycosis fungoides. Plaques and tumours in classic mycosis fibrosis occasionally ulcerate (figure 2), either spontaneously or after radiation therapy, prompting the need for aggressive care of the wound to prevent bacterial infection and sepsis.[25,26]

Sézary syndrome was classically characterised by the triad of generalised erythroderma (now defined as affecting >80% of body surface area; figure 1), lymphadenopathy and other systemic manifestations, and the presence of 5% or more malignant T cells with cerebriform nuclei (known as Sézary cells) in peripheral lymphocytes in the blood. However, the International Society for Cutaneous Lymphoma (ISCL) has recently proposed that the diagnosis of this disease be made primarily on the basis of molecular and flow cytometric evidence of a large clonal population of abnormal T cells in the blood in addition to erythroderma. Lymphadenopathy, although usually present, is now not regarded as essential to the diagnosis of Sézary syndrome. The bright red skin of these patients is often very pruritic. Many patients have fine scaling, and the palms and soles are often thickened, scaly, and fissured. Furthermore, these patients might develop alopecia, nail dystrophy, and eye changes (eg, blepharoconjunctivitis and ectropion) with advanced disease.[27]

Some patients with mycosis fungoides develop erythroderma, leading to a disorder termed erythrodermic mycosis fungoides.[28] Collectively, Vonderheid and colleagues[28] have used the term erythrodermic CTCL to include any of the lymphomas of primary skin and Sézary syndrome that evolve to erythroderma. Although Sézary syndrome and erythrodermic mycosis fungoides are sometimes difficult to distinguish clinically, patients with

mycosis fungoides are characterised by a history of mycosis fungoides and few (if any) abnormal cells in the blood generally. Only patients with true Sézary syndrome will have a substantial leukaemic T-cell burden in the blood.[28,29] Moreover, patients with this disease generally develop skin and systemic signs sooner, over months rather than years, than do those with erythrodermic mycosis fungoides.

Staging patients with mycosis fungoides and Sézary syndrome at initial diagnosis is helpful in guiding treatment[7] and it has prognostic value.[29,30] The lesions of mycosis fungoides and Sézary syndrome are classified into four tumour (T) groups: T1-patches and plaques affecting less than 10% of body surface area, T2-patches and plaques affecting more than 10% of body surface area, T3-presence of tumours (ie, raised, dome-shaped lesions >1 cm in diameter), and T4-erythroderma affecting more than 80% of body surface area.[31] Lamberg and Bunn[32] first described the overall staging, which is based on the tumour (T1–4), lymph node (N0–3), visceral metastasis (M0–-1), and blood (B0–-1) (TNMB) system. The ISCL has proposed that the B rating within the traditional staging system be expanded to include a B2 rating on the basis of molecular evidence of leukaemic involvement (table 2).[28,30] Since patients with extensive mycosis fungoides lesions (T2 or T3 disease) can have substantial blood involvement in the absence of erythroderma, blood assessment is needed in these patients.

Physicians should inform patients with mycosis fungoides that they do not invariably progress from one T stage to another. In fact, patients with T1 disease have an excellent prognosis and a healthy life expectancy compared with age-matched individuals.[33–35] Patients with T2 disease have a median survival of about 10–12 years and a 25% risk of progressing to more advanced disease.[35] Some patients initially present with advanced T3 stage disease, occupying an even greater risk category, although prognosis will vary depending on the histology and number of tumours. Extracutaneous (visceral) involvement identifies patients at high risk with median survivals of 1–2 years, whereas patients with only tumours or erythroderma have a median survival of 4–5 years.[30] Nodal enlargement is common, but does not necessarily suggest pathological involvement; its effect on prognosis is overshadowed by the extent of skin disease. The presence of increased numbers of CD8+ T cells in the skin is a favourable prognostic factor, presumably because this finding indicates a host antitumour response against the malignant CD4+ T cells.[36] Other histological features can be helpful in predicting which patients will rapidly progress from early-stage patch of plaque disease.[37]

Patients with erythrodermic CTCL have a substantially worse prognosis than do those with patch or plaque disease, and their prognosis is negatively affected by factors such as advanced age (>65 years), increased number of previous treatments, enlargement of peripheral lymph nodes, and greater leukaemic burden in the blood.[29,38]

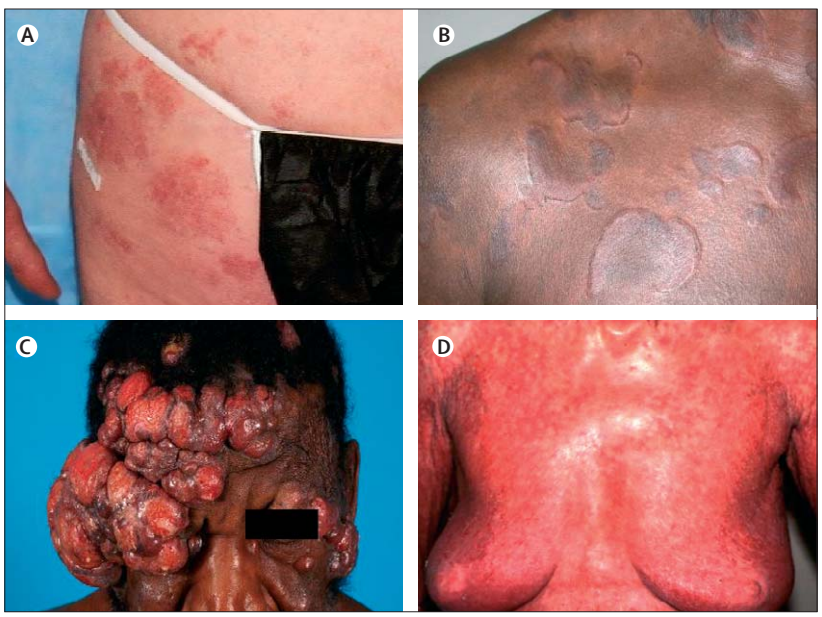

Figure 1: **Clinical manifestations of mycosis fungoides and Sézary syndrome**
(A) Patch-stage mycosis fungoides. (B) Plague-stage mycosis fungoides showing the arcuate accentuation of the borders in the thin-plaque lesions. (C) Tumour-stage mycosis fungoides. (D) Erythroderma in a patient with Sézary syndrome.

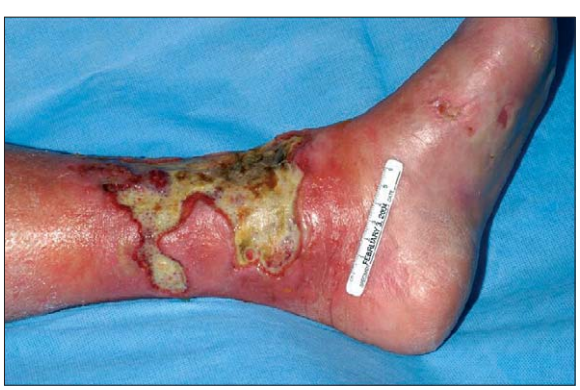

Figure 2: **Ulcerating plaque and tumour in a patient with mycosis fungoides**

Imaging with CT is routinely undertaken for patients with T3–4 disease to better assess visceral and nodal involvement, but is of lesser value in patients with T1–2 disease since internal organ involvement is rare without lymphadenopathy. PET can increase the sensitivity of detection of affected lymph nodes and can be useful to confirm response to treatment in patients with advanced disease.[39]

Diagnosis

Mycosis fungoides is characterised by the accumulation of mature (also termed peripheral) T cells in the skin. Malignant cells typically express CD4 and do not express cytotoxic protein markers,[5] although a substantial subset of neoplastic T cells has been reported to express cytotoxic protein markers.[40] Histologically, patches and plaques of mycosis fungoides often show band-like lymphocytic

	Clinical signs
Tumour stage	
T1	Patches/plaques <10% body surface area
T2	Patches/plaques >10% body surface area
T3	Tumours (rounded or dome-shaped lesions >1 cm in diameter)
T4	Erythroderma (>80% of body surface area affected)
Nodal stage	
N0	No clinically abnormal peripheral lymph nodes, pathological findings not CTCL
N1	Clinical abnormal (palpable) peripheral lymph nodes, pathological findings not CTCL
N2	No clinically abnormal peripheral lymph nodes, pathological findings positive for CTCL
N3	Clinical abnormal (palpable) peripheral lymph nodes, pathological findings positive for CTCL
Peripheral blood	
B0	Atypical circulating cells not present (<5%)
B1	Atypical circulating cells present (5% or more)
B2	Leukaemic involvement defined by absolute Sézary cell count ≥1000 cells per μL, CD4/CD8 ratio ≥10 by flow cytometry, aberrant expression of normal T-cell markers, molecular evidence of clonality, or chromosomal abnormality in a T-cell clone[28]
Visceral organs (M)	
M0	No visceral organ involvement
M1	Visceral involvement with pathological confirmation

CTCL=cutaneous T-cell lymphoma.

Table 2: **TNMB staging system for mycosis fungoides and Sézary syndrome[28,32]**

infiltrates in the upper dermis. Atypical T cells of small to regular size with irregular (cerebriform) nuclei are frequently present within the epidermis (ie, epidermotropism) (figure 3).[41,42] Pautrier microabscesses, consisting of aggregates of malignant T cells and epidermal dendritic cells (Langerhans cells) in the epidermis (figure 3), are a fairly specific but insensitive histological marker for mycosis fungoides.[42] Malignant T cells can also accumulate along the basal layer of the epidermis, showing a distinctive effect resembling a string of pearls (figure 3). Since histological findings in mycosis fungoides are often non-diagnostic, especially in patch-stage disease, serial biopsy samples are frequently needed for a definitive diagnosis. Tumours are composed of dense sheets of cytologically atypical lymphocytes in the dermis, commonly without the epidermotropism that is noted in patch or plaque disease (figure 3).

Immunohistochemical staining generally shows atypical CD4+ T cells (figure 3), although CD8+ mycosis fungoides does occur, particularly in children.[43] Ancillary findings such as loss of T-cell antigens (CD2, CD3, CD5, CD7, and CD26) or the presence of a clonal T-cell receptor (TCR) gene rearrangement by PCR can be helpful but might be non-specific.[44] In one large study, clonality was detected in the lesional skin of 83·5% of CTCL samples by PCR methods (compared with 2·3% of samples from patients with benign inflammatory skin disease).[45] Although detection of T-cell clonality correlates better with the cellular density than with the T score or immunophenotype,[45] it can nevertheless be useful for assessment of minimum residual disease after treatment.[46]

The diagnosis of early mycosis fungoides often needs integration of clinical, histological, and molecular features since it can be confused with benign eczematous skin disease.[47] The ISCL proposed a four-point scoring system (panel 2) with these components to aid the diagnosis of early disease, although its use has yet to be established.[42] The advantage of the system is the integration of four independent criteria, allowing diagnosis in the absence of some commonly observed features of mycosis fungoides.

The histology of Sézary syndrome in the skin is variable, and histological criteria for mycosis fungoides are sometimes not met. Sézary syndrome was historically associated with the presence of large, atypical lymphocytes with convoluted nuclear, called Sézary or Lutzner cells, in the peripheral blood. Cells that are morphologically similar to Sézary cells are found in the blood of healthy individuals and patients with inflammatory skin disease, leading to the notions that the Sézary cell is any atypical lymphocyte with a hyperconvoluted nuclei and that the Sézary cell is not specific for Sézary syndrome.[28,29,48] Thus, the ISCL proposed additional diagnostic criteria for this disease, which lists objective molecular evidence of blood involvement for the diagnosis and staging of Sézary syndrome in addition to the presence of Sézary cells, which are difficult to quantify by cytological analysis alone in many institutions (table 2).[28] Clonality within circulating lymphocytes (as measured by studies of TCR gene rearrangement by PCR) is a helpful criterion for confirmation of a diagnosis of Sézary syndrome, especially if the same clonal population can be detected in lesional skin. However, TCR clonality can also be detected in a large proportion of patients with autoimmune diseases such as systemic sclerosis[49] and in healthy older adults.[28] Flow cytometry is favoured to identify potentially malignant subsets (ie, through abnormalities of pan-T-cell markers or recognition of subsets of T cells expressing specific TCR Vβ epitopes) and to quantify response to treatment.[28]

Pathogenesis

Although several aetiologies have been postulated for mycosis fungoides and Sézary syndrome, their causes remain unknown. Chronic antigenic stimulation by pathogens such as *Helicobacter pylori* and hepatitis C virus has been associated with the development of gastric mucosal and non-Hodgkin lymphoma, respectively.[50,51] On the basis of limited experimental and clinical data, similar roles for skin-associated microbes such as *Staphylococcus aureus*[52] and *Chlamydia* spp[53] in terms of antigen stimulation of skin T cells have been postulated for mycosis fungoides and Sézary syndrome. The finding that patients with these disorders have a higher frequency of specific HLA class II alleles than do the general population lends support to the antigenic stimulation hypothesis,[54] but other definitive evidence is scarce.

Several groups have proposed a viral aetiology for mycosis fungoides, beginning with reports that a

truncated human T-cell lymphotrophic virus (HTLV)-1 sequence was present in skin biopsy samples of patients with this disease.[55] Although HTLV-1 is known to cause human adult T-cell leukaemia and lymphoma, many studies have reported little or no association between HTLV-1 and mycosis fungoides.[56,57] Other investigators have made associations between mycosis fungoides and Sézary syndrome, and the common cytomegalovirus[58] and Epstein-Barr virus.[59] Despite unconvincing data for the aetiology of mycosis fungoides and Sézary syndrome, a large body of evidence has accumulated regarding specific immune and genetic abnormalities in these diseases, perhaps leading to novel therapies that block the trafficking or proliferation of malignant T cells.

Immune abnormalities

Mycosis fungoides and Sézary syndrome represent malignancies of a skin-resident, CD45RO+ effector memory T cells[60] that have a unique expression pattern of chemokine receptors and adhesion molecules (eg, cutaneous lymphocyte-associated antigen [CLA]). Clark and colleagues[61] calculated that 98% of normal CLA+ effector memory T cells reside in skin. Although the bulk of normal skin-resident T cells are of T-helper-1 (Th1) phenotype and express chemokine receptors CCR4 and CCR6, smaller subsets such as central memory,[60] Th2, and T-regulatory cells also exist in the skin.[61] Such findings are consistent with the notion that mycosis fungoides and possibly Sézary cells are derived from CLA+ effector memory cells.

Evasion of immune recognition is a strategy that tumours adopt to ensure survival. In patch-stage and plaque-stage lesions, the malignant T cells represent a minority of T cells in skin. Non-malignant CD8+ T cells are often present and are associated with improved prognosis.[36,62]

Expression of Fas ligand by malignant T cells can help with the clearance of Fas-expressing CD8+ T lymphocytes that are tumour specific through direct contact and could explain the inverse relation between Fas ligand expression of malignant cells and the number of infiltrating CD8+ T cells in skin lesions of mycosis fungoides. A link has also been noted between increased amounts of Fas ligand expression and more advanced tumours, suggesting a role in tumour progression.[63] Such findings lend support to the notion that a host cytotoxic T-cell response against malignant T cells can slow disease progression.

Cytokine abnormalities

Malignant T cells in mycosis fungoides and Sézary syndrome respond to and synthesise cytokines in their local tumour microenvironment. Interleukins 7 and 18—but not interleukins 2, 4, 12, 13, or 15—are upregulated in the plasma and skin of patients with mycosis fungoides and Sézary syndrome.[64,65] In ex-vivo culture, interleukin 7 in lesions derived from mycosis fungoides was five times higher than it was in healthy skin. Furthermore, interleukin 7 was sufficient to enhance proliferation of healthy peripheral skin-homing T cells and was necessary to sustain malignant T cells from lesions of mycosis fungoides in vitro.[64]

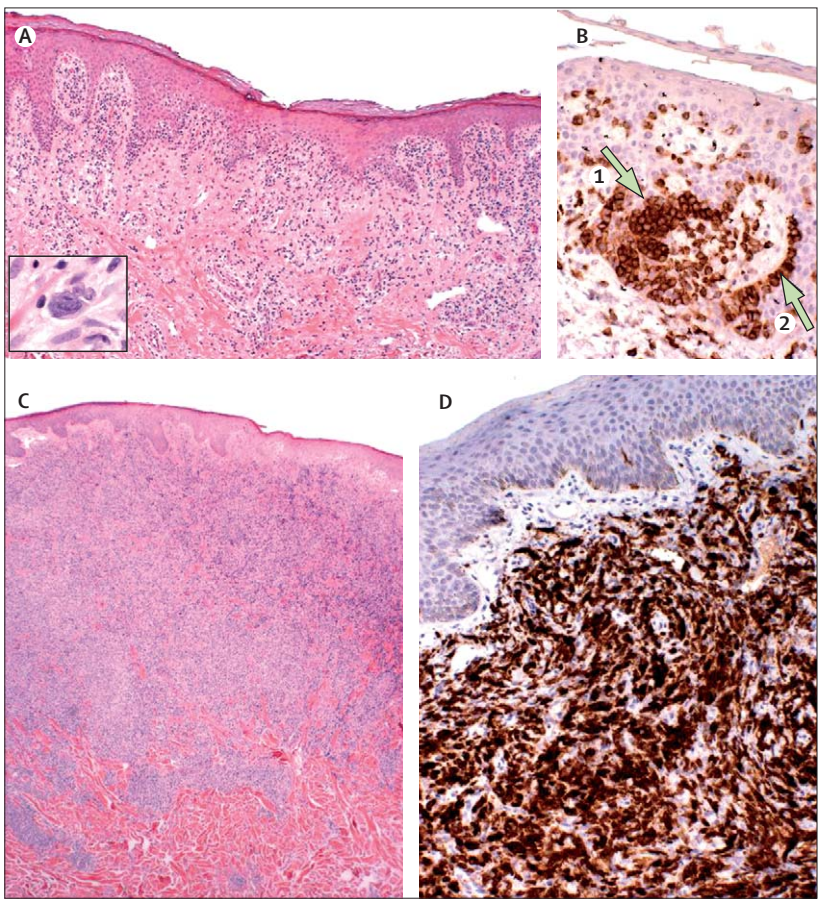

Figure 3: **Histopathological diagnosis of mycosis fungoides**
(A) Patch-plaque stage of mycosis fungoides shows atypical cells in the epidermis (ie, epidermotropism) and a band-like infiltrate of atypical T cells, often with cerebriform nuclei (inset), in the upper dermis. (B) CD2 staining is used to draw attention to mycosis fungoides cells that can aggregate together to form a Pautrier's microabscess (arrow 1). Malignant T cells might also line up along the epidermal basement membrane giving a "string of pearls" effect (arrow 2). (C) Histological appearance of tumour-stage mycosis fungoides after routine haematoxylin and eosin staining. (D) Histological appearance after CD4 immunostaining. This case of tumour-stage mycosis fungoides shows a substantial loss of epidermotropism.

Patients with Sézary syndrome and advanced mycosis fungoides are immunosuppressed, which is particularly evident in those with high-tumour burdens. Although the pathobiology of the immunosuppression is probably multifactorial,[66] an important factor could be Th2-skewing of T cells by interleukins 4 and 5.[67,68] Evidence also suggests that interleukin 18, a cytokine associated with atopic dermatitis (a Th2-predominant skin disease),[69] might contribute to the Th2 bias that is noted in mycosis fungoides and Sézary syndrome.[65] The importance of Th1 pathways in control of mycosis fungoides is suggested by the clinical efficacy of Th1-promoting cytokines such as interferon (IFN)-γ[70] and interleukin 12,[71] as well as by reports that aggressive cases of this disease have arisen after treatment with inhibitors of tumour necrosis factor α.[72]

Interleukin 15, which is overexpressed in mycosis fungoides and Sézary syndrome,[73] inhibits T-cell apoptosis after antigen exposure and promotes the expansion of CD4+ T cells[74] and Sézary syndrome cells.[75] Many cell types, including keratinocytes,[76,77] express interleukin 15 messenger RNA, but its protein expression is tightly regulated.[78] Moreover, before interleukin 15 can bind to its receptor on T cells, this cytokine is thought to be presented in trans via initial binding to the interleukin-15α chain of other cells, including epidermal Langerhans cells,[79] which can have several distinct roles in the pathogenesis of mycosis fungoides and Sézary syndrome.

Loss of T-cell repertoire

With PCR-based methods, Yawalkar and colleagues[80] reported that half of patients with stage I/II disease and all those with stage III or IV disease showed substantial reductions in T-cell receptor diversity compared with the highly diverse T-cell receptor repertoires that are expressed by normal peripheral T cells in the blood. Moreover, T-cell receptor excision circles—a remnant of the initial gene rearrangement in T cells that is used as a measure of T-cell expansions—are decreased in the blood of patients with CTCL at all disease stages,[81] suggesting that, in addition to malignant T-cell expansion, normal T-cell populations have expanded in response to the space left by the loss of other T-cell families.

The loss of T-cell diversity in early stage disease is especially noteworthy and could be connected with the origin of mycosis fungoides and Sézary syndrome. A reduction in T-cell repertoire has commonly been noted after infection with specific viruses such as HIV-1.[82,83] A narrowed CD8+ T-cell repertoire was recorded in mice who were serially infected with two slightly different viruses (lymphocytic choriomeningitis virus and Pichinde virus) that shared cross-reactive MHC class I-restricted peptide epitopes, although this finding did not occur when mice were serially infected with the same virus.[84] Although no definitive evidence exists for a specific viral aetiology in mycosis fungoides and Sézary syndrome, narrowing of the T-cell repertoire could result from cross-reactivity (ie, molecular mimicry) between a viral epitope that is recognised after infection with some viruses and an autoantigen in the skin that sustains T-cell activation. This hypothesis could account for the inability to detect specific viral pathogens in skin lesions of mycosis fungoides since the initial viral pathogen might have been effectively eradicated.

Antigen-presenting cells

Antigen-presenting dendritic cells can have an important role in the pathogenesis of mycosis fungoides and Sézary syndrome, especially in maintaining the survival and proliferation of malignant T cells.[85] Presumably, dendritic cells acquire either self-peptide or non-self-peptide antigen that is presented on MHC class II molecules on their surface to malignant T cells. Berger and co-workers[86] showed that dendritic cells lend support to the long-term culture of Sézary syndrome cells, are capable of ingestion of apoptotic T cells (including Sézary cells), and can present antigens that stimulate the development of immunosuppressive Forkhead box p3 (FoxP3)+, CD25+ T-regulatory cells. After ingestion of apoptotic cells, dendritic cells induce Sézary cells to show characteristic features of T-regulatory cells.[87] The notion that Sézary cells have T-regulatory activity might partially explain the immunosuppression noted in these patients, but in-vivo evidence is scarce.

Chemokine receptors and skin tropism of malignant T cells

The cutaneous tropism of the malignant T cells in mycosis fungoides and Sézary syndrome can be partially

***Panel 2*: Algorithm for diagnosis of early mycosis fungoides**

Clinical criteria

Basic

- Persistent and/or progressive patches or thin plaques

Additional

- Non-sun exposed location
- Variation in size or shape
- Poikiloderma

Scoring

- 2 points for basic criteria and two additional criteria
- 1 point for basic criteria and one additional criterion

Histopathological criteria

Basic

- Superficial lymphoid infiltrate

Additional

- Epidermotropism without spongiosis
- Lymphoid atypia*

Scoring

- 2 points for basic criteria and two additional criteria
- 1 point for basic criteria and one additional criterion

Molecular biological criteria

- Clonal TCR gene rearrangement

Scoring

- 1 point for clonality

Immunopathological criteria

- <50% CD2+, CD3+, and/or CD5+ T cells
- <10% CD7+ T cells
- Epidermal or dermal discordance of CD2, CD3, CD5, or CD7†

Scoring

- 1 point for one or more criteria

A total of four points is needed for the diagnosis of mycosis fungoides on the basis of any combination of points from the clinical, histopathological, molecular biological, and immunopathological criteria. *Lymphoid atypia is defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours. †T-cell antigen deficiency confined to the epidermis. Reprinted (with slight modification) from reference 42 with permission from The American Academy of Dermatology.

explained by their expression of specific chemokine receptors. Chemotactic cytokine (chemokine) receptors belong to a much larger family of G-protein-coupled receptors that span seven membranes.[88] The nomenclature of chemokine receptors and their chemokine ligands derives from their placement in one of four related families on the basis of the spacing of crucial cysteine residues.

CCR4 and CCR10 and their ligands play potential parts in homing of malignant T cells to skin. CCR4 and CCR10 are expressed by normal T cells with a skin-homing, CLA+ phenotype,[89,90] and are frequently present on cells of mycosis fungoides and Sézary syndrome.[91–94] Notably, CCL17—a major CCR4 ligand—is synthesised by activated keratinocytes, dendritic cells, and endothelial cells, and is increased in the serum of patients with mycosis fungoides.[95] CCR10 and its keratinocyte-derived ligand, CCL27,[96] have been implicated in the homing of CLA+ memory T cells to skin under inflammatory conditions.[89,90] Similar to CCL17, CCL27 is increased in the serum of patients with mycosis fungoides and Sézary syndrome and can indicate disease activity.[97,98]

The CCL17 and CCL27 chemokines induce T-cell arrest on the luminal side of blood vessels, followed by diapedesis through the endothelium, and migration along chemokine gradients produced by keratinocytes and immune cells that are present in the skin.[99] Most chemokine receptors activate downstream prosurvival pathways, including phosphatidylinositol-3-kinase and Akt (protein kinase B), leading to increased resistance to apoptosis.[100,101] Thus, chemokines not only change T-cell migratory properties and promote migration to the skin, but also enhance their survival (figure 4).

The CXCR4 chemokine receptor might also have a role in homing of Sézary cells. Loss of cell surface antigens such as CD7, CD26, and CD49d[66] are characteristic of mycosis fungoides and Sézary syndrome. Of particular relevance is the loss of CD26, also known as dipeptidylpeptidase IV, which proteolytically cleaves and inactivates CXCL12, the CXCR4 ligand.[102] Inactivation of CD26 enhances the migration of cell lines derived from patients with Sézary syndrome in response to CXCL12, whereas the addition of soluble CD26 is inhibitory.[103] With the presence of CXCL12 in skin, loss of CD26 on the Sézary cells can help with their cutaneous migration or enhance survival.

These results suggest that targeting receptors such as CCR4 and CCR10, which show expression on skin-homing T cells, can block the migration or survival of malignant T cells (figure 4). Although small-molecule antagonists of CCR4 and CCR10 have yet to be developed, antibodies to CCR4 can induce death of malignant T cells in vitro, albeit through antibody-dependent cellular cytotoxicity.[104] Fusion proteins that consist of a chemokine and a tumour-cell antigen have been used to target CCR6+, immature dendritic cells, leading to protective T-cell responses against lymphoma in mice.[105] Such chemokine-antigen fusion proteins take advantage of the physiological endocytosis of chemokine receptors after ligation, ultimately enhancing presentation of the peptides derived from antigenic tumours on the cell surface.[106] Chemokine-toxin fusion proteins analogous to the interleukin-2-diphtheria toxin-fusion protein (denileukin diftitox) could also be highly specific for some T-cell populations, resulting in endocytosis of the chemokine-toxin and cell death. Such fusion molecules could prove useful as therapeutic agents in mycosis fungoides or Sézary syndrome (figure 4).

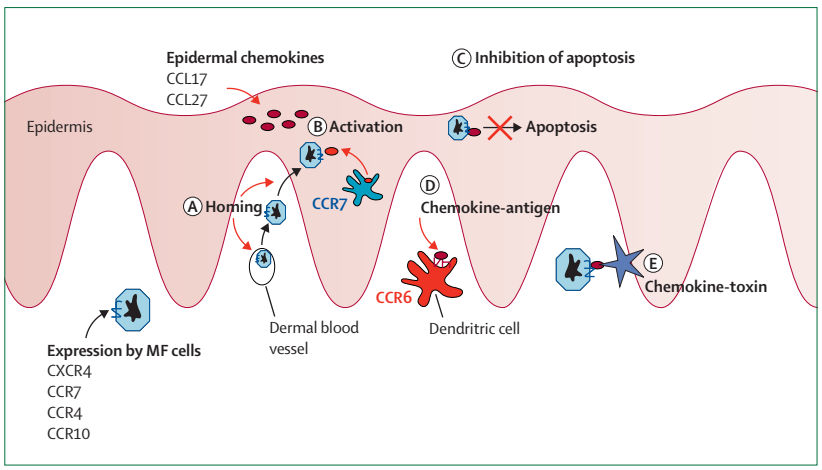

Figure 4: **Roles for chemokine receptors in mycosis fungoides**
Chemokine receptors can have important roles in the trafficking and survival of malignant T cells in the cutaneous microenvironment. (A) Homing: activation of T-cell integrins eases T-cell adhesion to skin endothelial cells and subsequent binding to extracellular matrix proteins. T cells migrate along a gradient of chemokines (eg, CCL17 and CCL27) to the epidermis. (B) Activation: chemokine receptors allow T cells to efficiently engage dendritic cells, such as Langerhans cells, resulting in T-cell activation and release of inflammatory cytokines. (C) Inhibition of apoptosis: chemokine-receptor engagement leads to up-regulation of PI3K and Akt, which are key prosurvival kinases. Activation of downstream effectors of this pathway can allow T cells to survive and proliferate in the skin environment. (D) Chemokine-antigen fusion proteins can be used to target tumour antigens from mycosis fungoides cells to CCR6+ antigen-presenting dendritic cells to stimulate host antitumour immunity. (E) Chemokine-toxin molecules can target specific chemokine receptors found on mycosis fungoides cells to mediate direct killing. MF=mycosis fungoides.

Advances in treatment

Since mycosis fungoides and Sézary syndrome are rarely curable, the goal of treatment is to control the disease while keeping toxic effects to a minimum. Many topical treatments (eg, nitrogen mustard, corticosteroids, and bexarotene) and ultraviolet light-based therapies readily control some patch and thin-plaque disease. Systemic treatment is appropriate for patients who are poorly controlled by topical therapy or who have widespread plaques and tumours. In patients with advanced disease or those who have failed many single-agent treatments, a combination or range of treatments incorporating photochemotherapy, retinoids, and biological drugs can be beneficial.[107] In particular, patients with Sézary syndrome might benefit from this varied approach, which has yielded overall response rates approaching 90%.[108] A complete discussion of the clinical management of mycosis fibrosis and Sézary syndrome is beyond the scope of this Seminar, but comprehensive reviews discussing therapy are provided

elsewhere.[7,109,110] We will focus on newer medical treatments for advanced mycosis fungoides and Sézary syndrome (summarised in table 3) and mechanisms of action.

Experimental therapies

Malignant T cells of mycosis fungoides and Sézary syndrome can retain varying degrees of responsiveness to pharmacological doses of biological drugs that blunt normal activated T-cell activity. For this reason, agents such as corticosteroids can have substantial activity, albeit usually of short duration. Topical corticosteroids are one of several effective therapies for early mycosis fungoides that is limited to the skin.[125] However, other imunosuppressants such as cyclosporine[126] and TNF-α antagonists[72] should be avoided in patients with these diseases because of reports of rapidly progressive disease after their use.

The overproduction of Th2 cytokines such as interleukins 4, 5, and 10 in mycosis fungoides and Sézary syndrome suggests that cytokines which promote a Th1 phenotype might be clinically useful. Interleukin 12, which is a Th1-promoting cytokine synthesised by phagocytic cells and antigen-presenting cells, enhances cytolytic T-cell and natural-killer-cell functions and is necessary for IFN-γ production by activated T cells. In vitro, interleukin 12 and IFN-α can inhibit synthesis of interleukin 5 by Sézary cells,[127] and interleukin 12 has shown clinical benefit.[71] Interleukin 12 is also being tested in combination with interleukin 2, which alone has a modest clinical response,[115] on the basis of their ability to upregulate their respective receptors and synergistically enhance T-cell or natural-killer-cell proliferation and cytolytic function.[128]

Recombinant IFN-α and IFN-γ can also shift the balance of the immune response from Th2 towards Th1 and have shown clinical activity (table 3). Of note, gene transfer of IFN-γ cDNA that is mediated by adenovirus has also been given intralesionally to induce tumour regression, keeping systemic side-effects associated with systemic use of the recombinant cytokine to a minimum.[129]

Antibodies to CD4 (zanolimumab) and CD52 (alemtuzumab) broadly target T cells and have shown clinical responses ranging from 38% to 78% in patients with mycosis fungoides and Sézary syndrome (table 3).[70,130] In phase II trials, alemtuzumab was effective in relieving erythroderma and pruritus in Sézary syndrome.[123] However, immunosuppression produced by alemtuzumab has been associated with serious infectious complications such as fatal mycobacterium pneumonia and generalised herpes simplex infection, especially in patients who have been heavily pretreated.[123]

Vaccine therapy

Vaccine immunotherapy for mycosis fungoides and Sézary syndrome is at an early stage. A scarcity of target antigens has hampered this work, but new antigens for

	Comments
TLR agonists	
CpG[111]	In-vitro stimulation of interferon-γ by PBMC
Imiquimod (TLR7,8)[112]	Clearance of plaques resistant to PUVA; induces interferon-α
CpG7909 (TLR9)[113]	Overall response rate of seven of 28 (25%)
Cytokine therapy	
Interferon-γ[70]	Five of 16 (31%) partial responses
Interferon-α[114]	Partial responses vary from 0–60% in many trials depending on several factors
Interleukin 12[71]	Overall response rate five of nine (56%); increased CD8+ T cells noted in regressing lesions
Interleukin 2[115,116]	Overall response rate of 18–71% depending on the study
Vaccine therapy	
Th1-skewing dendritic cells loaded with autologous tumour cells[117]	One patient, but impressive response in a patient who had failed all other therapies
Intranodal injection of dendritic cells loaded with autologous tumour cells[118]	Four patients with partial response, one with complete response, five with progressive disease
Mimotopes (non-natural peptides derived from combinatorial peptide libraries) screened for in-vitro stimulation of CD8+ T cells specific for CTCL cells[119]	Complete regression in two patients tested
Histone deacetylase inhibitors	
Depsipeptide[120]	Small trial with three partial and one complete response
Vorinostat [121]	24·2% response rate based on intent-to-treat analysis in heavily pretreated patients
Other targets	
AntiCD4 (zanolimumab, HuMax-CD4)[122]	Seven of eight patients with mycosis fungoides responded; average freedom from progression 25 weeks; no clinical evidence of immunosuppression
AntiCD52 (alemtuzumab)[123,124]	Overall response rate (38–55%) in 30 patients from two trials; could be particularly effective for patients with erythroderma (Sézary syndrome) and severe pruritus

TLR=toll-like receptor. PMBC=peripheral mononuclear blood cells. PUVA=psoralen and ultraviolet A. CTCL=cutaneous T-cell lymphoma. Th=T-helper.

Table 3: **Novel agents for treatment of mycosis fungoides and Sézary syndrome**

these disorders are being detected by novel serological screens with use of tissue cDNA libraries.[131] However, studies in animals and human beings of B-cell lymphoma suggest that dendritic cells pulsed with idiotype proteins (antigens) can elicit antitumour responses and tumour regression.[132,133] Cloning or synthesising the unique T-cell receptor sequences expressed by cells of mycosis fungoides or Sézary syndrome, analogous to the B-cell idiotype, is technically feasible and can provide a unique tumour target for immunotherapy.

One strategy to avoid cloning the T-cell receptor is to load autologous dendritic cells with tumour cells or lysates and inject them directly into a patient's lymph node.[118] Geskin and colleagues[117] showed that administration of autologous tumour-loaded dendritic cells treated with Th1-priming cytokines to heavily pretreated patients with Sézary syndrome resulted in beneficial clinical responses. Vaccination of patients with mimotopes, which are synthetic peptides (selected from combinatorial libraries) that stimulate antitumour CD8+ T cells, has also shown clinical benefit.[119]

Histone deacetylase inhibitors

Histone deacetylase inhibitors, such as depsipeptide[134] and vorinostat,[135] which has recently been approved by the US Food and Drug Administration, represent a new drug class for cancer treatment.[136] Mechanistically, histone deacetylase inhibitors induce growth arrest in conjunction with cell differentiation and apoptosis. Depsipeptide and vorinostat have shown notable clinical responses, especially in patients with Sézary syndrome who have had improvement in erythroderma (figure 5) and pruritus, and substantial decreases in the number of circulating Sézary cells.[135,137] Although mild electrocardiogram changes can arise after treatment with these drugs, they are not associated with increased cardiac troponin I or reduced left ventricular ejection fraction.[138] Treatment of the human T-cell lymphoma line, HUT78, with depsipeptide enhanced expression of interleukin 2 receptor and was synergistic with denileukin diftitox in an in-vitro cytotoxicity assay.[134] Conceivably, histone deacetylase inhibitors might be useful in combination with denileukin diftitox for more effective treatment.

Toll-like receptor agonists

Human toll-like receptors (TLRs) are a family of more than ten highly conserved pattern-recognition receptors that recognise a range of pathogen-associated molecules.[139] TLR9 recognises unmethylated, CpG-containing nucleotide motifs and is expressed within endosomes of plasmacytoid dendritic cells and B cells.[140] These motifs are present in most bacteria and DNA viruses but are uncommon in vertebrates. Upon activation by CpG oligodeoxynucleotides, plasmacytoid dendritic cells upregulate co-stimulatory molecules and migratory receptors, which probably promote migration to secondary lymphoid organs; generation of type I interferons by plasmacytoid dendritic cells might contribute to a strong Th1 immune response and enhance cellular immunity. Preliminary clinical studies of CpG oligodeoxynucleotides in mycosis fungoides and Sézary syndrome showed a response rate of 25%,[113] although CpGs as a drug class are probably most useful when used as adjuvants in immunotherapy or combined with cytotoxic drugs.[140] Imiquimod, a TLR7/8 agonist approved for use against genital warts, has been reported to clear plaques of mycosis fungoides that are resistant to psoralen and ultraviolet A.[112]

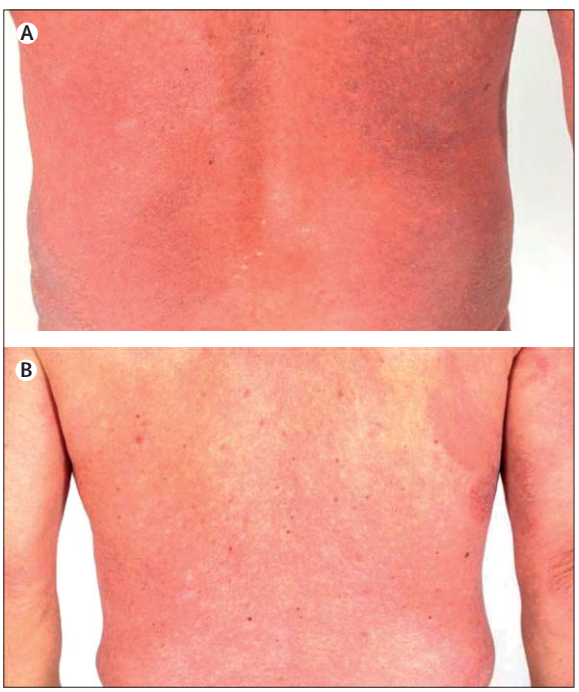

Figure 5: **Clearance of erythroderma in a patient with Sézary syndrome**
(A) Before and (B) after treatment with depsipeptide.

Selected approved agents for treatment

Bexarotene is a retinoid that modulates gene expression through selective binding to retinoid X receptors, forming either homodimers or heterodimers with other nuclear receptors that then act as transcription factors. Bexarotene is approved for use in both early-stage and late-stage disease as an oral drug for refractory disease, and as a topical gel in early-stage disease.[141] The pairing of bexarotene-bound retinoid X receptors and other nuclear receptors, such as the thyroid, peroxisome proliferator activation, and vitamin D receptors, probably contributes to its metabolic and hormonal toxic effects.[142] Bexarotene can be used at lower doses when combined with ultraviolet A light therapy, keeping common systemic toxic effects to a minimum while achieving comparable or improved clinical efficacy.[143]

Denileukin diftitox, a fusion molecule containing the interleukin 2 receptor binding domain and the catalytically active fragment of diphtheria toxin, targets the high-affinity interleukin 2 receptor that is found on activated T and B

cells.[144] Substantial toxic effects have been associated with denileukin diftitox.[145] In general, CD25-expressing tumours have a higher rate of response to denileukin diftitox than do CD25-negative tumours. Agents such as bexarotene, which up-regulate CD25 expression, seem to increase the response rate of denileukin diftitox.[146] Several clinical studies suggest that denileukin diftitox can deplete T-regulatory cells that have high interleukin 2 receptor expression, and potentially enhance endogenous anti-tumour immunity.[147,148] A newer agent, anti-Tac(Fv)-PE38 (LMB-2) (an anti-CD25 recombinant immunotoxin), contains an anti-CD25 Fv fragment that is fused to a truncated pseudomonas exotoxin; it has shown efficacy in mycosis fungoides and probably works via the same mechanism.[149]

Psoralen and ultraviolet A, as well as a narrow band ultraviolet B light, are effective in patch-stage and plaque-stage mycosis fungoides.[150] Treatment with narrow band ultraviolet B does not need oral psoralen, thus the systemic side-effects of the drug are eliminated. Ultraviolet light depletes skin Langerhans cells and impedes antigen presentation by dendritic cells, resulting in cutaneous immunosuppression.[151] Extracorporeal photochemotherapy (ECP) is another form of light treatment in which leucocytes treated with psoralen are exposed to ultraviolet A light as they pass through a narrow chamber ex vivo.[152,153] Heald and colleagues[154] have reported the efficacy of photopheresis in Sézary syndrome and erythrodermic mycosis fungoides.

The mechanisms underlying the efficacy of ECP are not completely understood. Berger and co-workers[155] have postulated that psoralen-treated malignant T cells exposed to ultraviolet A light ex vivo selectively undergo apoptosis and are then engulfed by dendritic cells upon re-infusion in patients. The antigen-loaded dendritic cells might then trigger a host response against the malignant T cells. However, the effects of ECP are likely to be more complex since this therapy can also be used to treat other diseases such as graft-versus-host disease, presumably by impairing immune response and increasing tolerance to foreign antigens.[156] Recent experimental and clinical evidence suggests that ECP can actually induce tolerance via the induction of antigen-specific T-regulatory cells.[157,158] In aggregate, these data suggest that ECP might trigger vaccine-like effects and induce T-regulatory cells, which could blunt proliferation of the malignant T cells.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank Mark C Udey and Edward W Cowen (Dermatology Branch, National Cancer Institute [NCI]), and Robert Knobler (Department of Dermatology, Medical University Vienna, Austria) for evaluating this manuscript and offering many helpful suggestions; Richard Piekarz and Susan Bates, National Cancer Institute, NIH, for provision of figure 5; and all the investigators who shared their data and ideas on the "Immunobiology and Immunotherapy of CTCL" at a workshop sponsored by the National Institutes of Health (Office of Rare Diseases) and the NCI May 6–7, 2006, in Philadelphia, PA, USA.

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