

REVIEW ARTICLE

Mycosis Fungoides and Sezary Syndrome

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MYCOSIS FUNGOIDES (MF) is an uncommon, indolent T-cell lymphoma first described by Alibert¹ in the early 1800s. It primarily involves the skin at early stages of the disease, with plaques being the typical feature. After a variable period of time, it may progress with development of cutaneous tumors and spread to visceral sites and lymph nodes (LNs).² Sézary syndrome (SS) is an erythrodermic variant of MF (MF) associated with the presence of circulating tumor cells in the peripheral blood.

Although MF/SS are often called cutaneous T-cell lymphomas (CTCLs) they should be differentiated from other non-Hodgkin's lymphomas that involve the skin such as peripheral T-cell lymphomas and adult T-cell leukemia/lymphomas. The diagnosis of MF rests on the clinical presentation as well as the histopathologic findings of an epidermotropic lymphoma with light microscopy showing a dermal infiltrate of lymphocytes with hyperconvoluted cerebriform nuclei and Pautrier's microabscesses. The malignant cells usually have a mature CD4⁺ T-helper cell phenotype. Because of the heterogeneity of both clinical and pathologic patterns, the diagnosis of MF is often difficult to make.

EPIDEMIOLOGY

MF and SS are the most frequent primary lymphomas involving the skin.² Over the last few years there appears to be an increasing incidence of this disease in the United States, with about 0.2 cases per 100,000 population in 1973 to 0.4 cases per 100,000 population in 1984.³ Therefore, there are about 1,000 new cases per year. Whether this represents a true increase in incidence or is attributable to a better awareness and hence more frequent recognition of this disease is not resolved.

Typically MF/SS is a disease of middle-aged adults, with the average age being about 50 years.⁴ However, there have been rare reports of children and adolescents who are affected,⁵ and it is not uncommon for the disease to be diagnosed in adults younger than 50 years of age. There is a 2:1 ratio of black people to white people and a 2.2:1 ratio of men to women with this disorder.³

ETIOLOGY AND PATHOGENESIS

The etiology of CTCL is unknown. Various theories implicate infectious agents, oncogenes, cytokines, or occupational or environmental exposures (Tables 1 through 3).⁶⁻⁹⁸ Clusters of cases within families have been reported.⁶¹ In general, however, MF is considered to be a sporadic disease without any real evidence of transmissibility. A synthesis of the available literature suggests that a pathogenic role for a variant or defective retrovirus is supported by the most convincing experimental observations, though the interpretation of some of these observations is still a matter of debate.

Viruses

Several viruses have been implicated in the pathogenesis of CTCL (Table 1). Perhaps the strongest data exist for

human T-cell lymphotropic virus-I/II (HTLV-I/II)^{7-9,11-16,18-20,62} (Table 1). Many investigators suggest that CTCL may have a viral etiology on the basis of certain similarities to adult T-cell leukemia, which is strongly associated with HTLV-1 infections.¹⁸ In fact, HTLV-I was originally isolated from a patient thought to have CTCL⁶² but who was later diagnosed as actually having adult T-cell lymphoma/leukemia.

Zucker-Franklin and Pancake⁷ recently reviewed the evidence for HTLV-I involvement in CTCL. Their most cogent arguments for such involvement include the following: (1) cultured MF/SS cells become immortalized and show virus particles indistinguishable from HTLV-I on electron microscopy¹⁷; and (2) polymerase chain reaction analysis (combined with Southern blotting) frequently demonstrates the presence of HTLV pol and/or tax sequences in MF/SS derived peripheral blood mononuclear cell lysate extracts.¹⁶ Even so, immunohistochemical studies of cultured MF/SS cells with morphologically evident HTLV particles do not consistently identify the particles as HTLV,^{6-7,13,16,18-20} and some investigators have failed to detect HTLV-I sequences in DNA derived from blood¹³ or skin¹⁹ of MF/SS patients. It is possible that these discrepant findings are due to variations in experimental methodology. Finally, the vast majority of patients fail to produce antibodies to HTLV I/II^{7-15,18} (although some of these patients may be seropositive for HTLV tax [the putative HTLV transforming gene¹⁶]). Of interest in this regard is that Hall et al¹⁸ detected the integration of HTLV-I provirus with major deletions in gag, pol, and env genes in seronegative MF patients. Their study suggests the possibility that patients with CTCL could harbor a defective or variant HTLV-I-like provirus. Moreover, it could be anticipated that although integration and presumably alteration of normal cell function occurs, the deletion may subsequently limit or prevent active replication. Thus, no antibody response or perhaps only a limited antibody response occurs.¹⁸

The human herpesviruses have also generated some interest in connection with MF.^{63,64} Herpes simplex virus (HSV) primarily targets epithelial and neural cells rather than lymphocytes. However, given the immunologic relationship between T lymphocytes and the epidermis and the fact that MF often appears to be initiated as a cutaneous process, a potential role of HSV in the development of progression of this malignancy seems plausible. The presence of both HSV-specific antigens and DNA in lesions of CTCL has been

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Table 1. Viruses in the Etiology/Pathogenesis of MF/SS

Mechanism	Comment	References
HTLV-I	Antibodies studies, have shown <1%-15% seropositivity for HTLV-I, though more of these patients may be seropositive for tax (the putative HTLV transforming gene).	6-17
	Cultured peripheral blood mononuclear cells from MF/SS patients become immortalized and show particles consistent with HTLV-I ultrastructurally.	17
	A defective HTLV may be involved since PCR studies by some (but not all) investigators have shown >90% positivity for HTLV I pol and/or tax sequences.	7, 16-20
HTLV-II	DNA extracted from peripheral blood mononuclear cells from one patient showed HTLV-II sequences.	21
HIV	CTCL (MF) seen in rare patients with HIV/AIDS, but the vast majority of MF patients are HIV.	22, 23
HSV I/II	In situ hybridization/indirect immunofluorescent techniques in lesional skin biopsies showed HSV I/II sequences in most of the patients.	24, 25
HHV-6	Case report of HHV-6 positivity by PCR.	26
EBV	100% positivity for EBV antibody in 21 patients v 60% positivity in 20 healthy controls.	27
	Most cultures of peripheral blood mononuclear cells from MF/SS patients elaborate EBV.	13

reported.^{24,25} However, no direct association between chronic infection with HSV and the development of malignant lymphoma has been shown.

Anecdotal cases of other viruses have also been studied in MF/SS. Brice et al²⁶ detected human herpesvirus-6 (HHV-6) in one patient with CTCL from a total of 30 patients in their study group and in one patient with lymphomatoid papulosis. Epstein-Barr virus (EBV) DNA has also been isolated from T-cell lymphomas.⁶⁵⁻⁶⁷ Lee et al²⁷ demonstrated anti-EBV antibodies in all of a series of 21 patients with CTCL compared with 12 of 20 healthy controls, and some investigators have noted the consistent emergence of EBV in cultured MF/SS lymphocytes (although this may be attributable to the ability of HTLV to reactivate latent EBV⁶⁸). Finally, Nahass et al²² reported a patient with acquired immunodeficiency syndrome (AIDS) and CTCL who was shown by polymerase chain reaction to be without concomitant HTLV-I infection. Zucker-Franklin et al⁶⁹ described two homosexual human immunodeficiency virus (HIV)-infected men with MF who harbored tax and pol HTLV-I proviral sequences in their blood and skin. Crane et al²³ also described four patients with AIDS or HIV infection who developed a CTCL. However, thus far lymphoblast cultures⁷⁰⁻⁷² and Southern Blot hybridization⁷³ from patients who had both AIDS and lymphoid malignancy have failed to show genomic intergration of HIV-1.⁷⁰⁻⁷³

Chromosomal Abnormalities

The few cytogenetics studies of patients with MF/SS which have been reported indicate that the predominant feature, especially in SS, is the multiplicity of chromosomal abnormalities (Table 2). The most common numeric change is loss of chromosome 10.²⁸ This abnormality is detected in 32% of SS cases. The most frequent structural aberrations in SS involve chromosomes 1 (43% of cases), 2 (43% of cases), 6 (38%), 9 (20%), 11 (25%), 13 (21%), 14 (27%), and 17 (34%).²⁸ The breakpoints tend to aggregate at 1p11, 1p36, 2p11-24, 6q, 9q, 11q, 13q11-14, 14q11, 14q32, and the pericentric region of 17.²⁸ A patient with a t(14;14)(q12;q13) translocation has also been described.⁷⁴

Oncogenes

The data on oncogene involvement in CTCL remain sparse and less than compelling (Table 2). P53, a tumor suppressor gene, has been found to be overexpressed (a finding suggestive of the presence of the mutant form) in some cases of high-grade CTCL, but rarely in low-grade CTCL.^{29,31} LYT-10, a member of the NF-KB family of transcriptional activators, and originally cloned by virtue of its involvement in a lymphoid malignancy-associated translocation,⁷⁵ is rearranged in a small proportion (2 of 29) of CTCL cases.³² In addition, structural defects of the long arm of chromosome 10 (10q24), the site of residence of LYT-10, have been described.²⁸ Finally, BCL-2, a gene which slows programmed cell death (apoptosis) and whose rearrangement is the hallmark of follicular lymphomas,⁷⁶ was expressed in 22 of 26 cases of MF, although expression was also seen in inflammatory disorders.³³ Because suppression of apoptosis by aberrant expression of BCL-2 or one of several other cell death genes is an important pathogenic mechanism in lymphomas,⁷⁷ further study of the molecular genetic regulation of apoptosis in MF/SS is warranted.

Environmental Toxins

Several investigators have hypothesized that atypical T cells in the skin of patients with CTCL proliferate in response to external stimuli provided by the local environment (including industrial or environment exposure to contact allergens).⁹⁴ Case series studies and ecological comparisons⁵⁰⁻⁵² have implicated a wide variety of agents including metals and their salts (chromium, mercury), halogenated hydrocarbons and aromatic hydrocarbons, plastics, and contact allergens (plants, cosmetics, hair dyes, insect bites). However, a large case control study by Whittemore et al⁴⁹ did not support the relationship between occupational or chemical exposures and CTCL risk, nor was there evidence of altered delayed cutaneous hypersensitivity or increase in atopy for patients with MF compared to control subjects.⁴⁹ This lack of relationship was also found in a study of 53 case-control pairs in Scotland.⁵³

Bacterial Superantigens

Investigators have shown⁵⁴ that Sézary cells respond in vitro to superantigenic exotoxins and that colonization by *Staphylococcus aureus* may influence disease activity (Table

Table 2. Etiology/Pathogenesis of MF/SS: Oncogenes and Environmental Factors

Mechanism	Comment	Reference
Chromosomal abnormalities	Most frequent structural changes in SS involve chromosomes 1, 2, 3, 9, 11, 13, 14, 17. Breakpoints aggregate at 1p11, 1p36, 2p11-24, 6q, 9q, 11q, 13q11-14, 14q11, 14q32, pericentric region of 17. The most frequent numeric change is loss of 10.	28
Oncogenes		
p53	Overexpressed p53 consistent with the presence of the mutant form may be present in some cases of high-grade CTCL but is rare in low-grade CTCL.	29-31
LYT-10	2 of 29 cases of CTCL had LYT-10 rearrangement.	32
BCL-2	BCL-2 expression found in 22/26 cases of MF but also found in inflammatory diseases	33
Occupational/ environmental exposure (Materials implicated include: metals and their salts, hydrocarbons, plastics, contact allergens)	Epidemiologic studies (case series, ecological comparisons) have shown an increased risk of CTCL, but two case-control studies showed no association between CTCL and such exposure.	49-53
Bacterial superantigens	Cutaneous colonization by <i>Staphylococcus aureus</i> may influence disease activity by CTCL.	54

2). In addition, treatment with antibacterial agents can attenuate erythroderma.⁵⁴

Cytokines and Growth Factors

Cytokines are a group of regulatory molecules that function as important mediators of cell communication, proliferation, and differentiation under normal and pathologic conditions. Several investigators have implicated a possible role of some of these molecules in CTCL (Table 3).

Interleukin-1 (IL-1). IL-1 consists of two biochemically different peptides, IL-1 α and IL-1 β .⁷⁸ IL-1 has potent biologic effects within the cutaneous microenvironment.⁷⁹ Human skin and cultured keratinocytes produce both IL-1 α and IL-1 β .⁸⁰ IL-1 receptor antagonist (IL-1RA) is a naturally occurring IL-1 inhibitor and is secreted by stimulated monocytes.⁸¹ The ratio

of IL-1RA to IL-1 α produced by keratinocytes may influence the relative inflammatory potential of IL-1 in the intact skin.⁸² It has been hypothesized that IL-1 may be involved in the compartmentalization of the lymphocytes to the skin by stimulating production of other cytokines such as IL-8⁸³ or inducing adhesion molecules.⁸⁴ Hansen et al,³⁵ using supernatants obtained from epidermal cell cultures, found a significant but small increase of IL-1 α protein release from involved CTCL epidermis compared to normal epidermis. Most of the IL-1 α release was derived from the keratinocytes. In a different study, Tron et al³⁶ found increased IL-1 β immunoreactivity using direct immunohistochemistry staining.

Soluble IL-2 receptors (sIL-2R). IL-2 is a glycoprotein synthesized and secreted by activated T lymphocytes. It promotes the proliferation of activated T cells by binding to IL-2 receptors.⁸⁵ sIL-2R functions as a physiologic inhibitor of

Table 3. Etiology/Pathogenesis of MF/SS: Cytokines, Histocompatibility Antigens, and Adhesion Molecules

Mechanism	Comment	Reference
Cytokines and growth factors		
IL-1	Some studies report increased IL-1 α /IL-1 β release from involved skin in patients with CTCL.	35-36
IL-2R	Increased levels may correlate with a poor prognosis.	37-42
IL-4	Increased levels of serum IL-4 found in patients with SS.	44
IL-6	Increased levels of IL-6-like material in lesional samples in CTCL patients.	45
IL-7	IL-7 induces significant growth (3- to 40-fold) of peripheral blood Sezary cells.	46
IL-8	Two studies showed increase IL-8 immunoreactivity in lesional biopsies from patients with CTCL (MF). However, another study failed to show an increase in IL-8 level.	35,47 42
IL-12	IL-12 production is deficient in SS.	48
TGF- β receptor II	Defective TGF- β receptor II expression on the surface of CD4 ⁺ SS cells.	34
Histocompatibility antigens		
HLA/B/C antigens	Some studies suggest an increased occurrence of Aw19, B8, Cw in patients with MF. However, these results were not confirmed by other studies.	55-56 57-58
HLA-DR	Increase in C locus antigen Cw1 reported in 1 study.	
	HLA-DR5 in 53% of patients with MF compared to 20% in control group.	58
Adhesion molecules		
	ICAM-1 is seen in lesional (but not in nonlesional) keratinocytes.	59
	Increased ICAM-1 on keratinocytes in plaque compared with leukemic stage.	60

IL-2.⁸⁶ Several reports³⁷⁻⁴⁰ have demonstrated elevated sIL-2R levels in patients with CTCL. For instance, Bernengo et al,⁴¹ after a 3-year follow-up of 17 patients with SS showed that increased sIL-2R serum levels correlated with clinical course and prognosis. Patients who had achieved a complete response after treatment were found to have almost a complete normalization of sIL-2R levels. Zachariae et al⁴² showed that sIL-2R levels of more than 1,000 U/mL correlate with clinical disease activity in patients with CTCL and confer a poor prognosis. Finally, Szeimies et al⁴³ reported a correlation between sIL-2R serum levels and stage of the disease, although this observation was not confirmed by Dummer et al.⁸⁷

IL-4. IL-4 has shown a broad spectrum of activities on both B and T lymphocytes. Recent studies⁸⁸ examining the cell growth characteristics from patients with CTCL indicate that IL-4 may be a significant cofactor for inducing proliferation. Increased IL-4 receptors have been reported on peripheral blood monocytes of patients with SS.⁴⁴ In addition, serum IL-4 levels were measured by enzyme-linked immunosorbent assay (ELISA) in 21 patients with SS; 33% had IL-4 levels significantly higher than those in control subjects.⁸⁹

IL-6. IL-6 enhances the production of acute-phase reactants and is required for T-cell proliferation.⁹⁰ Camp et al⁴⁵ showed increased levels of IL-6-like material in lesional samples from patients with CTCL. Their *in vitro* studies⁹¹ have shown that IL-6 induces human lymphocyte migration and affects both CD4⁺ and CD8⁺ T-cell populations. In another study by Lawlor et al⁹² in patients with MF, lesional IL-6 protein levels were also elevated.

IL-7. IL-7 is a stromal cell-derived factor that affects early lymphopoiesis.⁹³ IL-7 has shown to be mitogenic for resting thymocytes and stimulates proliferation of CD4⁻CD8⁺, CD4⁺CD8⁻, CD4⁻CD8⁻ cells.⁹³ Recently, Dalloul et al⁴⁶ have shown that IL-7 induces a 3- to 40-fold increase in growth of peripheral blood Sézary cells.

IL-8. IL-8 is both as a T-lymphocyte and neutrophil chemotactic cytokine.⁴⁷ Studies by both Hansen et al³⁵ and McLean-Wisner et al⁴⁷ have shown intense epidermal IL-8 immunoreactivity in lesional biopsies from patients with CTCL. However, Zachariae et al⁴² did not find any significant amounts of IL-8 in lesional specimens from patients in his study.

IL-12. IL-12 is a potent activator of cytotoxic T cells. Some investigators⁴⁸ have shown deficient production of IL-12 in peripheral blood mononuclear cells of SS patients compared with normal controls.

Transforming growth factor- β (TGF- β). SS cells exhibit a decreased response to the growth inhibitory effects of TGF- β accompanied by decreased expression of cell surface

TGF- β receptor II³⁴ (Table 3). However, at the intracellular level pools of TGF- β receptor II are comparable to those in normal CD4⁺ cells, indicating the presence of defective trafficking of this inhibitory cytokine receptor.³⁴

Major Histocompatibility Antigens (MHC) and Adhesion Molecules

Earlier studies^{55,56} that included small number of patients have suggested an increased occurrence of certain HLA antigens (Aw19, B8, Cw) in MF patients (Table 3). However, the above-reported results have not been confirmed by repeated studies.^{57,58} Data also exist for the relation of HLA-DR and CTCLs. For instance Safai et al⁵⁸ reported increased levels of HLA-DR-5 in 74 patients with MF. Studies have also shown that Langerhans cells⁹⁵ and keratinocytes⁹⁶ from patients with CTCLs both can express HLA-DR. Verga and Braveman,⁹⁷ in a report on 41 patients with CTCL, showed that 66% of those with active lesions had between 60% and 100% HLA-DR⁺ keratinocytes compared to 7% of individuals with psoriasis and 0% of healthy controls. Finally, CD1⁺ antigen-presenting cells in samples from the epidermis of MF patients have displayed an increased functional capacity to activate CD4⁺ nonmalignant T cells compared with CD1⁺ antigen-presenting cells from normal epidermis.⁹⁸ Furthermore, the level of class II major histocompatibility antigens is known to vary on these cells and may reflect their ability to activate T cells. Therefore, it is of interest that Hansen⁹⁸ showed that all three classes of MHC II molecules (HLA-DR, -DQ, -DP) are upregulated on CD1⁺ antigen-presenting cells in involved epidermis of patients with MF compared with those derived from normal epidermis. In contrast, the malignant T cells have different activation requirements because they can only be stimulated through antigen-independent pathways.⁹⁸ It has been suggested that the interaction between nonmalignant and malignant T cells may be important in the balance between remission and progression in MF.

The MHC II proteins, along with intercellular adhesion molecule 1 (ICAM-1), attract lymphocytes and, like the MHC II proteins, ICAM-1 can be shown in lesional but not in nonlesional keratinocytes in CTCL.⁵⁹ In addition, there is greater expression of ICAM-1 on keratinocytes in the plaque stage than in the leukemic phase, suggesting that loss of epidermotropism could be caused by less adhesive attraction between malignant cells and keratinocytes.⁶⁰

NATURAL HISTORY

Patients with MF/SS may have an extremely long natural history of disease. The condition may be confined to the skin for many years and is often preceded by indolent or

Fig 6. This lesion of Jessner's lymphocytic infiltrate of the skin shows parakeratosis (increased stratum corneum with retained nuclei) overlying the epithelium. There is mild acanthosis (thickening of the epidermis) and an absence of significant vacuolar alteration of the basal layer of the epidermis. There is edema and extravasated erythrocytes in the upper dermis. Extending from the papillary dermis deep into the reticular dermis is a confluent infiltrate of predominantly lymphocytes H&E, OM, $\times 25$). Immunoperoxidase studies (not shown) demonstrated positive staining of 95% of the lymphocytes with antibody to CD3 (T-cell marker), 5% of the lymphocytes with antibody to Leu 26 (B-cell marker), and none of the lymphocytes with antibody to CD30 (Ki-1).



Fig 1. Erythematous, scaling patches, and plaques of biopsy-confirmed MF on the right shoulder and proximal arm.



Fig 2. Biopsy-confirmed tumor lesions of mycosis fungoides appearing as hypopigmented and flesh-colored nodules on the head and neck.



Fig 3. Near-confluent erythroderma on the back and posterior arm of a patient with SS.



Fig 5. Biopsy-confirmed erythematous lesions of Jessner's lymphocytic infiltrate of the skin on the upper neck (arrow).

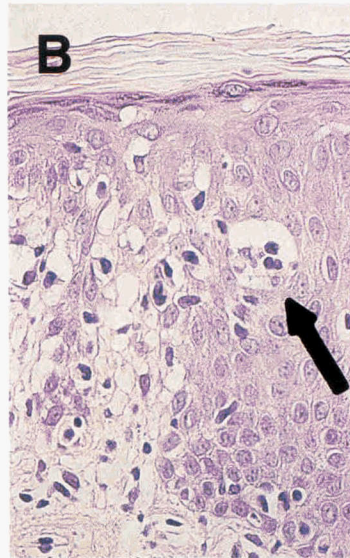
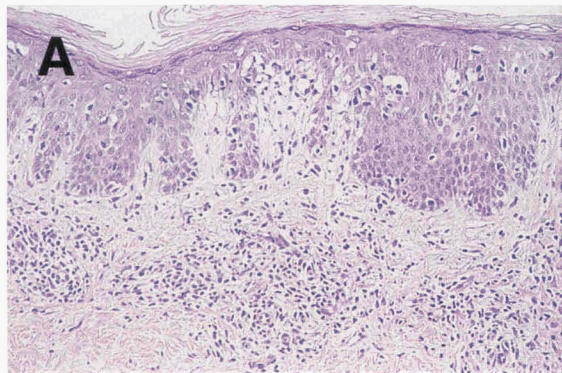


Fig 4. Distant (A) and closer (B) views of MF. There is a band-like infiltrate of atypical lymphocytes in the upper dermis (A). There is upward migration into epidermis (epidermotropism) of these lymphocytes as individual cells and small group of cells (Pautrier's microabscesses, arrow in B), (hematoxylin and eosin [H&E], original magnification [OM] $\times 50$ [A] and $\times 100$ [B].

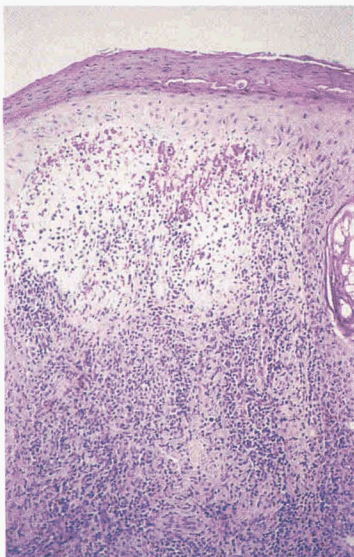


Fig 6.



Fig 7. Several hypopigmented annular scaling plaques of biopsy-confirmed parapsoriasis on the arm.



Fig 8. Erythematous nodules of biopsy-confirmed lymphomatoid papulosis on the medial leg.



Fig 10. Distant (A) and closer (B) views of biopsy-confirmed (central hole in B) follicular mucinosis showing patches of follicular prominence with hyperpigmentation and alopecia on the right thigh. The patient presented with lesions that did not improve after topical corticosteroid therapy. Eventually MF developed.

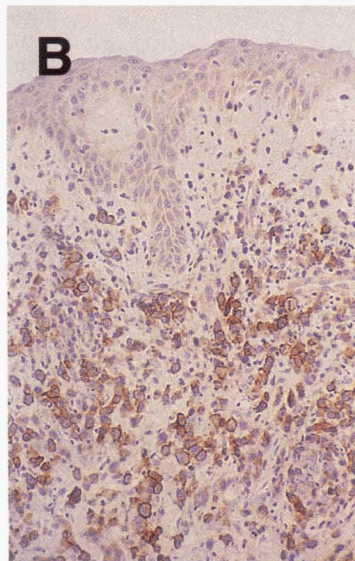
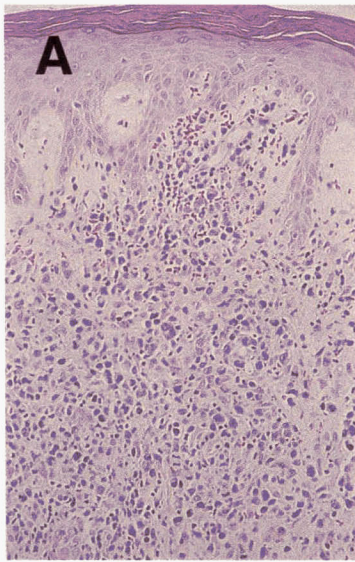


Fig 9.

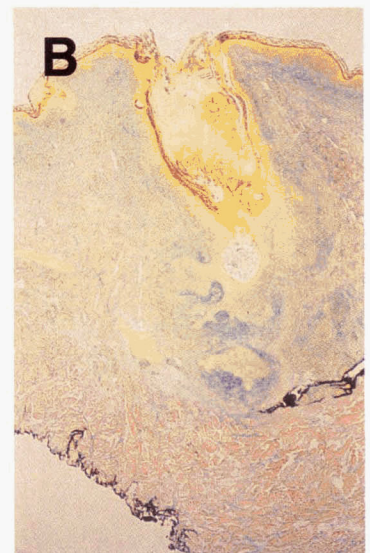
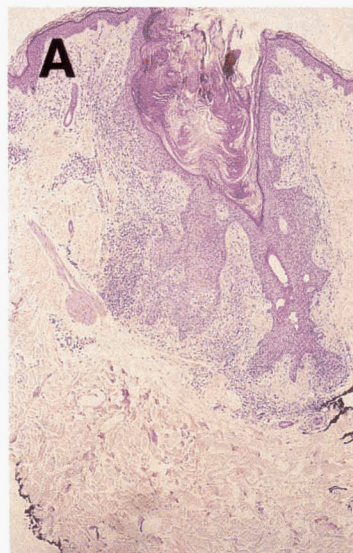


Fig 11.

pre-malignant phases which are difficult to distinguish reliably from benign cutaneous lymphoid infiltrates by routine histological criteria.⁹⁹ The median duration from the onset of skin symptoms to the diagnosis of MF/SS is nearly 6 years.¹⁰⁰ Patients with premycotic lesions should have regular follow-up with biopsy repeated as new lesions appear or the pattern of disease changes.

Characteristically MF evolves through several clinical stages. The earliest phase is the patch phase characterized by the presence of slightly scaling, erythematous, flat patches; as patches become more infiltrated they evolve into palpable plaques. Plaques are usually erythematous, slightly scaling, and have well-margined borders (Fig 1). In some individuals there is a prominent involvement of the palms and/or soles with hyperkeratosis and fissuring of the skin. Patches and plaques usually have an asymmetrical distribution, particularly around the hips, buttock, lower trunk, groin, axillae, and breasts. The lesions tend to be broad (>1 cm in diameter and often >5 cm) and are frequently pruritic.^{100,101} If left untreated, infiltrated plaques may evolve into ulcerated exophytic tumors (Fig 2). Generalized dermal thickening can also develop, and when present in the facial area may result in a leonine facies.

Tumors are the initial presentation in approximately 10% of patients (d'emblée presentation).¹⁰² Although some patients with premycotic or patch phase of skin involvement never show evidence of progression to other types of skin lesions during their lifetime, many eventually will progress to more advanced stages of the disease. It is also very common for patients to have patch and/or plaque and/or tumor stage disease present simultaneously at different areas at their skin. The rapidity of progression from patches to plaques to tumors is variable and unpredictable.

Sézary syndrome is characterized by a pruritic exfoliation or infiltrated erythroderma accompanied by circulating Sézary cells (Fig 3).^{103,104} The number of circulating atypical cells necessary to define the syndrome and the best method to identify Sézary cells are not well delineated. Erythroderma may be the only manifestation of skin involvement or else there may be superimposed plaque or tumors. Also sometimes noted is generalized lymphadenopathy and/or splenomegaly. Circulating Sézary cells are present in approximately 25% of patients with cutaneous tumors, 10% of patients with generalized plaques, and the majority of patients with erythroderma.¹⁰⁵ Despite circulating Sézary cells, the bone marrow is often negative for disease.

Extracutaneous visceral involvement is more evident clinically as the stage or extent of CTCL increases.¹⁰⁶ The major

route of extracutaneous spread is to regional lymphatics and the viscera.¹⁰⁰ The peripheral LNs are the most frequent site of extracutaneous involvement by CTCL (40% to 70% depending on the series).¹⁰⁷⁻¹⁰⁹ Most often, node involvement can be detected as peripheral lymphadenopathy. Occult splenic and liver infiltration has been reported (34% and 16%, respectively).¹⁰⁶ Pulmonary involvement in CTCL is usually asymptomatic; it may present as mediastinal or hilar adenopathy, parenchymal nodules, or pleural effusion.¹¹⁰ Because marrow infiltration is often subtle, bone marrow can appear to be uninvolved even in the presence of significant numbers of circulating Sézary cells.^{111,112} On autopsy, the most common sites of visceral involvement are spleen, lung, and liver (about 50% each).^{4,112}

Infection is very common and remains the major cause of death in patients with MF/SS. The most frequently isolated organisms are *Staphylococcus aureus* and *Pseudomonas aeruginosa*.^{100,101,113} In addition, in our experience, staphylococcal septicemia is especially common in these patients in the presence of indwelling central lines (R.K., unpublished data).

HISTOPATHOLOGY

Histopathologic features of the skin are similar in both MF and SS and have been defined by the International Lymphoma Study Group.¹¹⁴ MF/SS is characterized by marked epidermotropism of cytologically atypical T lymphocytes, with convoluted cerebriform nuclear contours.¹¹⁴ These cells collect in clusters known as Pautrier's microabscesses in the epidermis and in bandlike infiltrates of the upper dermis (Fig 4), circulate in the blood, and involve the paracortex of LNs. The infiltrate is accompanied by interdigitating and Langerhans' cells.¹¹⁴ Infiltration of the visceral organs with malignant lymphocytes can frequently be seen several years after the initial skin penetration.¹¹⁵

A wide histologic spectrum can be found in MF/SS. In a recent study, Shapiro and Pinto¹¹⁶ reviewed 222 biopsy specimens of MF/SS and concluded that CTCL produces almost all the patterns for diagnosing inflammatory disease, at times making the distinction between MF and inflammatory disorders difficult. The most common pattern in plaque stage disease was the superficial perivascular, which is also the most common pattern seen in inflammatory skin disease. The second most common pattern was superficial and deep perivascular. Various viewpoints^{117,118} have been advanced regarding the utility of lymphocytic atypia in the diagnosis of early stage disease. Shapiro and Pinto¹¹⁶ noted atypical lymphocytes in about half of cases whereas Nickoloff¹¹⁹ noted atypia in 100% of cases.

Fig 9. There is parakeratosis overlying the acanthotic epithelium of this lesion of lymphomatoid papulosis. Within the dermis there is a dense confluent infiltrate that consists of numerous large atypical lymphocytes that have hyperchromatic, irregularly shaped nuclei [A] H&E, OM × 50. Immunoperoxidase studies show that the dermal infiltrate consists only of CD3 (T-cell marker)-positive, Leu 26 (B-cell marker)-negative cells (not shown) and that many of the atypical cells stain with antibody to CD30 (Ki-1) [B] immunoperoxidase with antibody to CD30, OM × 50.

Fig 11. This lesion of follicular mucinosis (alopecia mucinosa) is characterized by a keratin-plugged follicle, a perifollicular lymphocytic infiltrate, and mucinous degeneration of the outer root sheath and sebaceous gland cells that create cystic spaces in the lower portion of the follicular epithelium the presence of mucin both adjacent to and within the follicular epithelium [A] H&E, OM × 10. The blue staining in the dermis adjacent to the hair follicle and within the area that has undergone reticular degeneration in the pilosebaceous apparatus of the follicle confirms the presence of mucin [B], colloidal iron, OM × 10.

Later tumor lesions are clinically nodular because there is a dense infiltrate of tumor cells within both the upper and lower dermis, which may extend into the subcutis. In these lesions the epidermis may be unaffected by tumor cells; these cells appear to have lost their epidermotropism.

The malignant cell in MF is of T-cell lineage. In most instances, the cells express the pan-T markers CD2, CD3, and CD5.^{120,121} The early T-cell marker CD7 may be deleted,¹²² but is positive in about one third of patients.¹¹⁴ The vast majority of cases of MF/SS are CD45⁺RO⁺CD4⁺ (memory helper T cell). These cells also express the skin homing protein termed cutaneous lymphoid antigen (CLP).³⁸ Occasional rare reports of CD8⁺ (suppressor T cell) MF have been described.^{120,123} The latter may be more aggressive than the CD4 type.¹²³ CD25 (IL-2 receptors), although negative in at least half the cases, may also be expressed.⁴⁰ Based on the cytokines expressed, it has been suggested⁸⁹ that MF exhibits a Th1-type profile and SS exhibits a Th2-type profile. The molecular biologic demonstration of dominant T-cell clonality (with Southern blot analysis and T-cell receptor- β [TCR- β] or TCR- γ gene rearrangement) has been used to establish or confirm a diagnosis of CTCL. However, in early lesions of MF (patch stage), where the number of infiltrating T cells is minimal,¹²⁴⁻¹²⁷ Southern blotting fails to consistently detect clonal T-cell populations.^{128,129} In these cases, polymerase chain reaction amplification of TCR gene rearrangement has been required to detect the dominant T-cell clone.¹³⁰ Therefore, the detection sensitivity of Southern blotting of DNA derived from skin biopsy specimens of early lesions is too low and may fail as a diagnostic test in early lesions, when the clinical and histologic diagnosis is most difficult. It is also important to emphasize that the demonstration of a monoclonal T-cell population, per se, cannot be equated with the diagnosis of CTCL. For instance, a monoclonal population may be the result of local expansion of stimulated cells (especially in the cases where low-intensity bands are detected) or may reflect one of the MF-like syndromes described below.¹³¹ Therefore, clinicopathologic correlation is essential.¹³²

PRECURSOR LESIONS AND RELATED LYMPHOMAS

It is very important to distinguish malignant lymphoproliferative disease from atypical lymphoid proliferations or abnormal immune responses that closely mimic malignant lymphomas. Table 4^{100,114,118,133-188} describes a number of conditions, some of which overlap one another, that can either precede or occur concurrently with MF, or can simulate MF. Broadly, these conditions can be subclassified into those that are almost always benign (actinic reticuloid, Jessner's infiltrate, and cutaneous pseudo-T-cell lymphoma), those that may progress to malignancy in a significant proportion of patients (large plaque parapsoriasis, lymphomatoid papulosis, alopecia mucinosa, and poikiloderma atrophicum vasculare), and those that are malignant (granulomatous slack skin syndrome, primary cutaneous CD30⁺ (Ki-1⁺) large cell lymphomas, and peripheral T-cell lymphomas). In addition, B-cell lymphomas and myeloid leukemias can also involve the skin. However, cutaneous B-cell lymphomas will show Ig light-chain restriction or rearrangement and will

express pan-B antigens such as CD19, CD20, and/or CD22, whereas myeloid leukemias infiltrating the skin can be distinguished by their morphology and myeloperoxidase positivity.

Actinic Reticuloid

Actinic reticuloid is a term used to describe those cases of severe, chronic, photosensitivity dermatitis that may eventually evolve to erythroderma. They have some clinical and histopathologic resemblance to MF/SS,¹⁶¹ although they are benign. A lymphoid infiltrate of mixed composition is seen.¹⁶⁰ There is often a predominance of CD8⁺ cells,¹⁶⁰⁻¹⁶² although predominant T-helper cell infiltrates have also been described.¹⁶⁰ The etiology of the photosensitivity may be a persistent T-cell immune response.¹⁶⁰

Jessner's Infiltrate

Clinically most lesions are papular, nodular, or plaque-like, often solitary, and may resemble tumor-stage MF (Fig 5). They usually occur on the face or upper trunk. Pathologically, the cardinal feature of Jessner's infiltrate is fairly well-circumscribed patches of lymphocytic (T-lineage) infiltrate around defined blood vessels with sparing of the epidermis (Fig 6).¹⁶⁵ TCR- β rearrangement may or may not occur.^{166,167} There are anecdotal reports of transformation to malignant lymphoma.¹⁶⁵

Cutaneous Pseudo T-Cell Lymphomas

Cutaneous pseudolymphomas are benign lymphocytic infiltrates that mimic B-cell or less commonly T-cell lymphomas clinically or histologically. Rijlaarsdam et al¹⁶⁸ studied the features of this disorder in 20 patients with entities other than lymphomatoid papulosis and actinic reticuloid. Half of the patients had solitary lesions (papules, nodules, or plaques) whereas the other half had more widespread disease. In six patients the pseudolymphoma was associated with the use of anticonvulsant drugs. In all 20 patients, the skin lesions cleared within 6 months, either spontaneously, with local steroid treatment or after stopping the anticonvulsant drug use. Lymphoma did not develop in any patient after a median follow-up of 48 months. Histologically two patterns were seen: (1) a subepidermal bandlike infiltrate of cerebriform lymphocytes without epidermotropism or Pautrier's microabscesses; and (2) a nodular or diffuse, mixed cell dermal infiltrate with a strong histiocytic component. The cells were usually CD2⁺, CD3⁺, CD4⁺, and CD5⁺. It has been reported¹⁶⁶ that TCR rearrangement can be present, indicating clonality. Therefore, differentiation between pseudolymphomas and lymphomas requires attention to both clinical and pathologic characteristics. Clinical characteristics suggesting pseudolymphoma include solitary lesions and spontaneous regression. CD30⁺ anaplastic lymphomas can also undergo spontaneous regression. However, pseudolymphomas are CD30⁻.¹⁶⁸

Large-plaque Parapsoriasis

Patients with large-plaque parapsoriasis exhibit slightly scaly, erythematous, atrophic patches with or without poiki-

Table 4. Skin Conditions Resembling or Related to MF/SS

Name	Characteristics	Histology	Relation to MF	Reference
Actinic reticuloid (AR)	Severe chronic photosensitivity dermatitis; may evolve to erythroderma.	Infiltrates contain T cells and Langerhans cells.	Benign course despite clinical and histological similarity to MF/SS.	160-162
Jessner's infiltrate	Solitary papules, plaques, nodules, usually on face and upper trunk.	Dense dermal collection of T cells with epidermal sparing.	Clinically may resemble tumor-stage MF.	165-167
Cutaneous pseudo T-cell lymphoma	Solitary lesions simulating MF. They often show spontaneous disappearance and can be associated with drug, especially anticonvulsant, use.	Benign bandlike or nodular pattern lymphocytic infiltrates of skin that simulate lymphomas.	Single lesion, spontaneous disappearance, no Pautriers microabscesses or epidermotropism favor pseudolymphoma.	166, 168
Large plaque parapsoriasis	Erythematous, atrophic lesions usually on trunk and buttocks.	Upper dermal nonspecific infiltrate. Immunophenotyping identical to plaque-stage CTCL.	10% of patients progress to MF over 10 years.	118, 133-135
Lymphomatoid papulosis (LP)	Continuous self-healing eruption. Red-brown papules which scale, crust, or necrose and resolve.	Patchy epidermal parakeratosis, acanthosis, spongiosis. Dermal perivascular lymphohistiocytic infiltrate.	10-25% associated with lymphoma (CTCL, Hodgkin's or CD30 ⁺ large cell) in most series. Total risk may be 80% at 15 years.	144-151
Alopecia mucinosa	Hair loss and indurated plaques and papules.	Acid mucopolysaccharides in sebaceous glands and hair follicles with periappendageal T-cell infiltrate. Band-like dermal lymphocytic infiltrate, cytologic atypia, no eosinophils favor MF.	Over 15% of patients will develop MF.	152-159
Poikiloderma atrophicans vasculare	Reticulate hypo/hyperpigmentation, telangiectasia, and skin atrophy. May resolve on exposure to sunlight but recur in winter.	Basal layer vacuolization, lymphocytes, thinned epidermis, a bandlike (lichenoid) infiltrate, dilated papillary dermal vessels.	Progression to CTCL associated with induration of skin and development of papules and plaques.	163-164
Pagetoid reticulosis	1. Worringer-Kolopp disease is localized variant with solitary skin lesion and indolent growth. 2. Ketrion-Goodman is generalized type with hyperkeratotic plaques.	Epidermal infiltration by large atypical T-cell (CD4 ⁺ or CD8 ⁺ or CD4 ⁻ /CD8 ⁻) proliferation.	1. Worringer-Kolopp may be localized variant of MF. 2. Ketrion-Goodman may have more unfavorable prognosis.	100, 136-142
Granulomatous slack skin	Large regions of slack skin accompanied by fibrotic bands.	Malignant cells palisading around zones of necrobiotic degeneration.	Variant of tumor-stage CTCL.	143
Primary cutaneous CD30 ⁺ large cell lymphomas	Localized papules, nodules, or tumors in the skin.	Predominant (>75%) or large clusters of CD30 ⁺ cells on biopsy.	Primary cutaneous CD30 ⁺ (Ki-1 ⁺) lymphomas are distinct from MF but subset of MF become CD30 ⁺ .	169-174
Adult T cell leukemia/lymphoma	Aggressive skin, blood, nodal disease with immunodeficiency, hypercalcemia. HTLV-1 causative.	IL-2 receptor (Tac ⁺) lymphocytes in blood and skin.	May resemble MF/SS clinically and histologically.	2, 175-186

lodermatous change, that cannot be distinguished clinically from patches of MF (Fig 7). They are usually larger than 6 cm and tend to occur on the trunk and buttocks. Studies have documented a progression of large-plaque parapsoriasis to overt MF in approximately 10% of patients over a 10-year period.¹³³ Immunophenotyping shows that large-plaque parapsoriasis and MF are indistinguishable,¹³⁴ and Staib and Sterry¹³⁵ showed TCR- γ rearrangement in 11 of 22 patients. Some investigators believe that large plaque parapsoriasis is actually a form of early MF.¹¹⁸

Lymphomatoid Papulosis

Lymphomatoid papulosis is a disease originally described by Macaulay in 1968¹⁴⁴ as a "continuous, self-healing eruption," which is clinically benign and histologically malignant. This disease is characterized by erythematous papules or nodules that progress to form vesicular crusted or hemorrhagic lesions and then undergo spontaneous healing with scarring (Fig 8).¹⁴⁵ Lesions tend to appear in groups and individual lesions resolve in 3 to 4 weeks. The proliferation is histologically malignant and may possess any or all of the

features of T-cell malignancy. At the pathologic level two types of lymphomatoid papulosis have been described.¹⁴⁶ Type A is the large cell type in which component cells are CD30⁺ (Ki-1⁺) (Fig 9) and may resemble Reed-Sternberg cells. The pathology cannot be easily differentiated from that of anaplastic large cell lymphoma. Type B is the small-cell type reminiscent of MF. The lesions are usually positive for TCR- β rearrangement.^{147,148}

Lymphomatoid papulosis cannot be definitely diagnosed by pathologists without pertinent clinical information. In particular, the patient should be observed for spontaneous regression of the skin lesions because this is one of the features of the disease. In most series^{149,150} about 10% to 25% of patients develop frank lymphoma. However, Cabanillas et al¹⁵¹ reported that the cumulative risk increases with time and approaches 80% at 15 years. The lymphomas that develop include CTCL, Hodgkin's disease, anaplastic large cell lymphoma, and T-cell immunoblastic lymphoma.

Alopecia Mucinosa

Pinkus¹⁵² is credited with reporting the original description of patients with alopecia mucinosa (also known as follicular mucinosis). At early stages, lesions are centered on follicles and hair loss may be an early sign (Fig 10). Evolution to indurated papules and plaques eventually occurs. This inflammatory disorder is characterized by the accumulation of acid mucopolysaccharides in sebaceous glands and root sheaths of hair follicles in conjunction with a periappendageal T-cell infiltrate (Fig 11).¹⁵³ TCR- β rearrangement consistent with a clonal T-cell population can be seen.¹⁵⁴ At least 15% of patients with alopecia mucinosa, especially those with disseminated disease, also have CTCL.¹⁵⁵⁻¹⁵⁷ In other patients with alopecia mucinosa, clinically and histologic identical lesions will develop but the course will be benign. There is also an adolescent/pediatric form which is more benign.¹⁵⁸ Thus far clinical and histologic features have failed to distinguish patients with primary alopecia mucinosa from those with alopecia mucinosa and CTCL. In some cases the presence of follicular lesions may not be associated with mucinosis but might result from involvement of hair follicles by lymphoma cells. This condition is called follicular mycosis fungoides.¹⁵⁹

Poikiloderma Atrophicans Vasculare

Poikiloderma atrophicans vasculare is characterized by reticulate hypopigmentation and hyperpigmentation, telangiectasia, and skin atrophy. The eruption may resolve on exposure to sunlight during summer but recur in winter. Basal layer vacuolization, increased numbers of lymphocytes in the thinned epidermis, a lichenoid infiltrate and dilated blood vessels in the papillary dermis (on routine microscopy), and deposits of immunoreactants at the basement membrane (using immunofluorescent microscopy) are seen in the skin biopsy specimen.¹⁶³ Cutaneous lupus erythematosus is the most important differential diagnosis. Progression to CTCL is associated with induration of the skin and development of papules and plaques.¹⁶³ Samman¹⁶⁴ showed that 9% of patients with poikiloderma died of lymphoma during the period of observation.

Pagetoid Reticulosis

Two different forms of pagetoid reticulosis have been recognized. The benign localized type first described by Woringer and Kolopp in 1939¹³⁶ presents with a slowly developing, solitary, cutaneous hyperkeratotic plaque; the disseminated type, reported by Ketron and Goodman in 1931,¹³⁷ displays erythematous psoriasiform patches, nodules, and ulcerated skin tumors, and usually has a worse prognosis.¹³⁸ Pathologically, the cardinal feature of pagetoid reticulosis is infiltration of the epidermis by large atypical mononuclear cells. This disease has been shown to have a proliferation of monoclonal T cells.¹³⁹ Some consider the Woringer and Kolopp variant to be an indolent, localized, hyperkeratotic variant of MF.¹⁴⁰ After treatment, Burns et al¹⁴¹ observed disease-free periods of 18 months to 17 years. However, in contrast with MF and other CTCLs, the neoplastic T-cell infiltrate express a CD3⁺, CD4⁻, CD8⁻ or a suppressor cytotoxic CD3⁺, CD4⁻, CD8⁺ phenotype in about 50% of the reported cases.¹⁴² Often its differentiation from MF is based on clinical grounds.¹⁰⁰

Granulomatous Slack Skin

Granulomatous slack skin is a rare syndrome in which patients develop redundant skin folds accompanied by fibrotic bands in areas such as the axilla and groin. This disorder has been shown to be a monoclonal T-cell lymphoproliferative disease of CD4⁺ cells. Histology shows malignant cells palisading around zones of necrobiotic degenerated connective tissue. TCR- β rearrangement is seen,¹⁴³ indicating clonality. Characteristic multinucleated giant cells may help to distinguish granulomatous slack skin from tumor lesions of MF.¹⁴³

Peripheral T-Cell Lymphoma

T-cell lymphomas remain difficult to subclassify.¹¹⁴ However, their origin can be grouped into those expressing thymic antigens (such as lymphoblastic lymphomas) or postthymic antigens. Nonepidermotropic, postthymic T-cell lymphomas represent the diverse group of peripheral T-cell lymphomas.¹⁸⁷ These can be further subclassified as low to high grade,¹⁸⁸ and often behave aggressively. The International Lymphoma Study Group¹¹⁴ has recently tackled their subclassification and suggested that four subtypes, ie, angioimmunoblastic T-cell lymphoma, angiocentric lymphoma, intestinal T-cell lymphoma, and adult (HTLV-1⁺) T-cell leukemia/lymphoma, can be reliably recognized as distinct entities. The majority of cases of peripheral T-cell lymphomas in Japan and the Caribbean are HTLV-1⁺. However, in the United States and Europe few cases (0% to 10%) have HTLV-1 infection.¹⁸⁷

Adult T-cell leukemia/lymphoma is believed to be caused by HTLV-I retroviral infection.^{2,175-180} It generally affects individuals 30 to 60 years old, and often has an acute and aggressive course. Lymphadenopathy, hepatosplenomegaly, fever, leukocytosis due to increased T cells, hypercalcemia, lytic bone lesions, pulmonary infiltrates, and opportunistic infections are common.¹⁸¹⁻¹⁸³ About 50% of cases present with rapidly developing skin lesions that resemble MF/SS

both clinically and histopathologically.^{176,183} A more chronic form with cutaneous, LN, and blood involvement has also been described.^{176,177} The lymphocytes in the blood and skin generally express high levels of IL-2 receptors. The epidemiologic, cytologic and clinical features, along with seropositivity for HTLV-1, help to differentiate this entity from MF/SS.¹⁸⁴⁻¹⁸⁶

The clinical presentation of non-HTLV-1⁺ peripheral T-cell lymphomas is heterogenous. There is a high incidence of skin and extranodal involvement (especially of the upper aerodigestive tract), widely disseminated disease, and systemic symptoms. Skin lesions can take the form of maculopapular lesions, nodules, plaques, and ulcers.¹⁸⁷ Some patients present with lesions initially restricted to the skin.

Primary Cutaneous CD30⁺ (Ki-1⁺) Large Cell Lymphomas

Primary cutaneous CD30⁺ large cell lymphomas (both anaplastic and nonanaplastic) represent a distinct category of cutaneous large cell lymphomas that arise de novo in the skin and have a relatively good prognosis. Histologically they are defined by predominant (>75%) or large clusters of CD30⁺ blast cells in the skin biopsy.¹⁶⁹ They are distinct from cutaneous CD30⁺ lymphomas that have developed in a preexisting CTCL such as MF^{170,171} or lymphomatoid papulosis,^{170,172} and from CD30⁺ large cell lymphomas that represent cutaneous localization of a primary noncutaneous CD30⁺ large cell lymphoma. However, the differentiation between these entities is not always clearcut. Most patients with primary cutaneous CD30⁺ lymphoma are adults and have solitary or localized skin lesions (papules, nodules, or tumors) at presentation.¹⁶⁹ Only a small proportion (10%) of these patients have extensive skin disease.¹⁶⁹ Development of extracutaneous disease, usually in the LNs, is observed in a minority of patients.¹⁶⁹ In some patients, spontaneous regression of skin lesions occurs.¹⁶⁹ Most patients with primary cutaneous CD30⁺ large-cell lymphomas have a favorable prognosis with a 4-year survival rate of 90%.^{169,170,173} Radiotherapy is often used as therapy. However, in patients with MF, development of CD30 positivity may confer a worse prognosis.^{170,174}

TRANSFORMATION OF CTCL

Transformation of CTCL was initially described by Lukes and Collins.¹⁸⁹ Overall, 8% to 55% of patients with CTCL undergo transformation.^{174,189-192} Transformation may involve cutaneous or extracutaneous sites. Morphologically, there is transformation from small- or intermediate-sized cerebriform cells to large cells.^{174,191} Clinically, transformation usually occurs in patients with advanced stages. However, it may be noted at any stage of disease. In a study by Greer et al¹⁹⁰ of 113 patients, 9 patients had transformation at diagnosis. The median time from diagnosis to transformation is generally about 1.5 years.^{190,191} Median survival from transformation was 27 months compared to 53 months in patients without transformation in the study by Greer et al.¹⁹⁰ The prognosis was even worse in the study by Dmitrovsky et al,¹⁹¹ with the median survival from transformation being

only 2 months. Indeed, CTCL that has transformed to large cell lymphoma may represent an additional stage of the disease (accelerated form). In general, transformed CTCL retains the helper T-cell phenotype,¹⁹² although T-suppressor and aberrant T-subtype phenotypes may be noted.¹⁷⁴ Transformation of CTCL often involves decreased expression of pan T-cell antigens (CD2, CD3, CD5) and increased expression of activation markers (Ki-1, Leu-M1, LN2).¹⁷⁴

STAGING AND PROGNOSIS

A Tumor-Nodes-Metastases (TNM) staging system (by the MF Cooperative Group [MFCG]) for MF/SS was proposed in 1979.^{100,193-198} (Table 5). This system takes into account the percent body surface involved, type of skin manifestations (patches/plaques or tumors of erythroderma), and the presence or absence of LN or visceral organ involvement. The involvement of the peripheral blood does not influence the stage in this classification. The extent and type of skin involvement and the number and sites of palpable LNs correlate reasonably well with the prognosis (Table 5).¹⁹³⁻²⁰³

Depending on the series, about 20% to 50% of patients present with limited plaque (T1) disease, 25% to 35% with generalized plaque (T2), 15% to 25% with tumor involvement (T3), and about 10% to 20% with erythroderma (T4).^{100,197,201} Extracutaneous disease has generally been considered a manifestation of advanced CTCL. However, in autopsy series, the majority of patients (including many without clinical evidence of visceral involvement) are found to have extracutaneous disease.^{4,112}

Initial work-up of all patients should include history and physical, documentation of all skin lesions, complete blood counts with Sézary count, serum chemistries, and skin biopsy. A LN biopsy should be performed if nodes are enlarged. Computerized tomographic tests, bone marrow aspirates and/or biopsies, and invasive tests add little in the early stages of the disease, but can be useful for baseline assessment in patients with more advanced skin or blood disease.¹⁹³ Lymphangiograms are rarely warranted regardless of the stage.

Sausville et al²⁰⁰ have proposed a modification of the TNM staging system based on histopathologic evaluation of skin, LNs, blood, and visceral sites. They were able to identify three distinct prognostic groups of patients. Good-risk patients were those with plaque skin disease, negative peripheral blood smear, and no evidence of visceral disease or nodal disease; this subgroup had a median survival of more than 12 years. Poor-risk patients were those with positive visceral disease or effaced LNs, and their median survival was 2.5 years. The intermediate-risk group included all the remaining patients; this subgroup had a median survival of 5 years. Multivariate analysis indicated that visceral involvement and advanced skin disease (T3 and T4) were the most important independent prognostic factors.²⁰⁰

LN histopathologic class has also been suggested as a significant determinant of survival. Fuks et al²⁰⁴ showed that patients with palpable adenopathy had an inferior prognosis compared with those who did not, even if their LN biopsy samples showed only dermatopathic lymphadenopathy. Several studies have evaluated the potential predictive value of

Table 5. Staging and Prognosis: TNM Classification System

T Skin	10-yr Survival (%)	5-yr Survival (%)
T1 Limited plaques (<10% body surface area)	80	91
T2 Generalized plaques	50	72
T3 Cutaneous tumors	20	35
T4 Generalized erythroderma	30	46
N Lymph Nodes	M Visceral Organs	
N0 No adenopathy, histology negative	M0 no involvement	
N1 Adenopathy, histology negative	M1 Visceral involvement	
N2 No adenopathy, histology positive		
N3 Adenopathy, histology positive		

Stage	Definition	5-yr Survival (%)
I	Limited (<10%) IA, or generalized plaques (IB), without adenopathy or histologic involvement of lymph nodes or viscera (T1N0M0 or T2N0M0).	80-90
II	Limited or generalized plaques with adenopathy (IIA) or cutaneous tumors with or without adenopathy (IIB); without histologic involvement of lymph nodes or viscera (T1-2N1M0, T3N0-1M0).	60-70
III	Generalized erythroderma without (IIIA) or with (IIIB) adenopathy; without histologic involvement of lymph nodes or viscera (T4N0-1M0).	40-50
IV	Histologic involvement of lymph nodes (IVA) or viscera (IVB) with any skin lesion and with or without adenopathy (T1-4N2-3M0 for IVA, T1-4N0-3M1 for IVB).	25-35

Summarized from references 100, 193-198.

the histologic patterns of LN involvement. Sausville et al²⁰¹ have proposed a system of grading LN involvement in patients with MF/SS based on the number of atypical lymphoid cells in paracortical zones and evaluation of LN architecture. This staging was found to correlate with the extent of skin, blood, and visceral involvement as well as with survival.²⁰¹ Patients with LN1 (reactive node) or LN2 (dermatopathic node, small [<6 cells] clusters of convoluted cells) have a median survival more than 90 months.²⁰⁰ The 5-year survival for LN2 is 70%.^{193,201} Those with dermatopathic changes and large (>6 cells) clusters of convoluted cells (LN3) have a 5-year survival rate of 30% (median survival, 55 months).²⁰⁰ Individuals with nodes effaced by frankly neoplastic lym-

phocytes (LN4) have a 5-year survival rate of only 15%.²⁰¹ (median survival = 30 months.²⁰⁰ On the other hand, Vonderheid et al^{202,203} have suggested that there is no significant survival difference in patients with the different levels (LN1 to LN3) of uneffaced nodes. These investigators reported that the unequivocal histologic presence of tumor cells in the nodes is, however, highly predictive of survival. Patients with involved nodes had a median actuarial survival of 53 months as opposed to 137 months for patients with uninvolved nodes. Survival was calculated from the time of the initial skin biopsy. Therefore, these investigators²⁰² devised a classification system to define prognostic subgroups of patients with LNs demonstrating frank neoplasia. Patients

Table 6. Response to Treatment in MF/SS: Topical Therapy, Phototherapy, and Radiation Therapy

Modality	Response Rate (CR + PR)	CR Rate	Duration of Response	Comment	Reference
Topical nitrogen mustard	>70%	30-60%	About 1/3 of patients with CRs have long-term remissions.	Patients with limited-stage disease had higher response rates and remained disease-free for longer periods.	109, 207-210
PUVA	>75%	51-88%	Generally up to 3 yr with maintenance therapy.	Significant number of patients relapse after discontinuation of treatment. More patients with early stage disease have prolonged remissions.	211-223
Photopheresis	54-75%	15-25%	48 mo (median) in 1 study. Not reported in other studies.	Best responses in patients with erythroderma.	224-232
TSEB	80-100%	36-98%	2-10 yr (median)	Higher CR rates and longer duration of response in limited-stage disease.	107, 233-239

Abbreviations: CR, complete response; PR, partial response; PUVA, psoralen (8-methoxypsoralen) and ultraviolet A light; TSEB, total body external beam radiation.

with LNs effaced with small cerebriform cells (low-grade subtype) had a better median survival (40 months) compared to patients with high-grade immunoblastic nodes (median survival = 9 months) or to those with intermediate grade involvement (median survival = 26 months).

Within the group of patients with erythrodermic MF (SS), Kim et al¹⁹⁹ have recently reported several prognostic factors. Patient age at presentation (≥ 65 years), overall clinical stage (IV rather than III), and circulating Sézary cells count ($\geq 5\%$ of total lymphocyte count) was associated with a worse prognosis in a multivariate analysis. Patient's symptoms duration and LNs status were significant in univariate but not in multivariate analysis. Patients were assigned to unfavorable (two or three poor prognostic factors), intermediate (one poor prognostic factor), or favorable (no poor prognostic factors) groups. The median survival was 1.5, 3.7, and 10.2 years, respectively ($P < .005$).

Finally, several investigators have examined biologic features of the disease as prognostic factors. sIL-2 receptors levels have been shown in many studies³⁷⁻⁴³ to correlate with clinical disease activity in patients with CTCL and increased levels may confer a poor prognosis. Expression of the tumor suppressor gene p53 also has been proposed as a prognostic factor because high expression (consistent with the presence of the mutant form) is seen in high-grade but not in low-grade CTCL.^{29,30} In addition, Hoppe et al²⁰⁵ have shown a correlation between a high proportion of CD8⁺ (T suppressor) cells in skin biopsy samples and better survival rates. They hypothesized that these cells may have an antitumor effect. However, transformation to large cell lymphoma and acquisition of CD30 positivity may be associated with a poor outcome.¹⁷⁴ Finally, Marti et al²⁰⁶ correlated T of TNM and serum LDH levels with survival rates.

THERAPY

A multitude of therapeutic strategies have been tried in MF/SS, and the results of many of them are summarized in Tables 6 and 7.^{109,207-296} Treatment regimens in early MF/SS are generally directed toward skin lesions, ie, psoralen and ultraviolet A (PUVA), topical chemotherapy (nitrogen mustard), and electron beam irradiation. Each topical approach has various advantages and disadvantages (as discussed below), but they generally produce similar response rates, and there are no randomized trials demonstrating superiority for one regimen over another. There have also been many trials with systemic treatment such as single agent or combined chemotherapy in MF/SS. However, in a randomized study aggressive therapy has not shown a survival advantage over conservative topical management as initial therapy for MF/SS.²³⁸ Photophoresis, retinoids, interferons (IFNs), ILs, and monoclonal antibodies have also been used with variable success rates (Tables 6 and 7).

Topical Chemotherapy

Topical mechlorethamine hydrochloride-nitrogen mustard (HN2) has been used for more than 30 years.²⁰⁸ It involves daily applications to all skin surfaces (except eyelids, lips, and rectal and vaginal orifices) for about 6 to 12 months to

achieve a complete response (CR). In several studies involving large numbers of patients^{109,207,209,210} the CR rate after treatment with nitrogen mustard ranged from 30% to 60%. This range reflects the initial extent of skin involvement. Patients with the limited plaque phase of skin involvement had CR rates of 50% to 60% and those with more advanced disease, especially stage IV, rarely achieve CRs. The curative potential of topical nitrogen mustard treatment also appears to be greater among patients who present with the limited plaque phase of skin involvement. Duration and frequency of maintenance treatment differ among institutions. Hoppe et al¹⁰⁹ continue treatment to 1 to 2 years after complete remission. Ramsay et al²¹⁰ continue treatment for 6 months after skin clearing and then tapered the treatment during the next 1.5 years. Vonderheid et al²⁰⁹ recommended only 6 months of ongoing therapy.

Adverse reactions to nitrogen mustard include contact irritant dermatitis, dry skin, hyperpigmentation, and telangiectasias, as well as an increased risk of squamous cell and basal cell skin cancers. When applied in a water vehicle, hypersensitivity to topical nitrogen mustard occurs in up to 40% of patients and limits its use. Dilution can sometimes help desensitize the skin, and hypersensitivity is less common with the use of an ointment base.²⁷⁵

Despite impressive response rates and occasional long disease-free intervals, most patients treated with topical treatment relapse. For this reason systemic treatment alone or combined with topical treatment has been used.

PUVA

This regimen consists of the ingestion of psoralen in the form of 8-methoxypsoralen (a photosensitizing drug) followed by exposure to high-intensity, long-wave ultraviolet A (UVA) irradiation. Psoralen intercalates with DNA after UVA exposure and forms crosslinks between DNA strands, thus interfering with DNA synthesis. Therapy is usually administered three times per week for 3 to 6 months followed by tapering.

Numerous studies have confirmed the efficacy of PUVA for clearing early-stage CTCL, as well as the benefit of maintenance therapy in prolonging remission.²¹⁴⁻²¹⁹ The Scandinavian MF/SS study group reported that in 51 patients with plaque-stage MF treated with aggressive doses of PUVA, a CR rate of 58% was achieved within 4 to 12 months. Patients remained in remission for 9 to 53 months on maintenance therapy.²²⁰ Another report from the same group of investigators evaluated the efficacy of PUVA in patients with tumors. Complete or partial clearing was noted in 14 of 17 patients.²²¹ In 82 patients with predominantly stage I disease, Herrmann et al²¹³ reported a response rate of 95% with a CR rate of 65% (mean duration of CR = 43 months). Roenigk et al²²² report long-term data on 82 patients with a mean follow-up of 45 months. Complete clearing with PUVA was seen in 88% of patients with limited plaque stage, and 52% with extensive plaque disease. No patients with tumor stage disease had complete clearing. A significant frequency of relapse was noted in all stages when PUVA was discontinued or changed to maintenance. Therefore, these investigators

Table 7. Response to Treatment in MF/SS: Chemotherapy and Bioimmunotherapy

Modality	Response Rate (CR + PR)	CR Rate	Duration of Response	Comment	Reference
Single-agent chemotherapy	62%	33%	3-22 mo (median)	Multiple active agents. The most data exist for methotrexate.	224, 295
Combination chemotherapy	81%	38%	5-41 mo (median)	Multiple combinations have been used.	224, 237-239
Autologous BMT	83%	83% (5 of 6 patients)	3 of the CRs lasted <100 d; 2 CRs continue at 1 yr	Small number of patients.	240-241
Adenosine analogues					
DCF	33-67%	7-33%	1.0-16+ mo		242-244
2CDA	13-47%	14-20%	Median = 3-4.5 mo		245-247
FAMP	19%	3%	Not reported		248
Cyclosporin	32%	0%	2.4-24 mo		249-253
IFN- α	55%	17%	4-28 mo (median)	Dose response has not been shown.	224, 254-255, 296
Retinoids	58%	19%	3-13 mo (median)		224
IFN- α + Retinoids	60%	11%	Usually less than 1 yr		224
IFN- α + PUVA	90%	62%	Median = 28 mo (range, 1-64 mo)		222, 256
IFN- α + DCF	41%	5%	Median = 13.1 mo		257
IFN- α + FAMP	51%	8%	Median = 6 mo		258
MoAbs	11%	0	Not reported		224, 259-269
IL-2	5 of 7 patients	3 of 7 patients	6+, 28+, 33+ mo for the CRs	Very small number of patients.	270
Immunoconjugates					
DAB ₄₈₆ IL-2	21%	Not clear	17 mo (median)	Small numbers of patients.	271-274
DAB ₃₈₉ IL-2	45%	9%	Not reported		271-274

Abbreviations: Autologous BMT, autologous bone marrow transplantation; CR, complete response; DAB, 3,3'-diaminobenzidine; DCF, 2-deoxycycoformycin; FAMP, fludarabine monophosphate; MoAbs, monoclonal antibodies; PR, partial response.

recommended aggressive maintenance PUVA in all patients even when they are clear.

Given the high relapse rate with PUVA alone, combination adjunctive therapy has also been used. Topical nitrogen mustard has been applied to clear areas of disease that are relatively shielded from PUVA.²²³ When Thomsen et al²⁷⁶ used retinoids with PUVA, the CR rate was equal to PUVA alone. However, the addition of retinoids reduced the number of PUVA treatments required to achieve remission as well as the total UVA dose needed, and the duration of remission seemed more prolonged if maintenance with retinoids was given. Investigators^{222,256} have also combined PUVA with IFN- α . When 39 patients with all stages of MF were treated, a CR rate of 62% and partial response (PR) rate of 28% was achieved (total response rate = 90%). The median response duration was 28 months.

PUVA is well-tolerated. Side effects may include nausea, dry skin, and erythema due to phototoxicity. More serious

concerns are an increased incidence of cutaneous carcinomas, especially squamous cell,^{277,278} and cataract formation. UV light blocking eyeglasses should be worn by all patients for 24 hours after administration of psoralen.

Photophoresis (Extracorporeal Photochemotherapy)

Photophoresis combines oral administration of 8-methoxypsoralen with extracorporeal UVA irradiation of peripheral blood. This procedure is performed on 2 consecutive days at 4-week intervals with clinical evaluation at 6 months to determine response. Those who show clinical improvement are maintained on this treatment schedule until maximum clearing. Afterward an additional 6 months of treatment is given, and the patient is then gradually weaned off therapy.^{225,230-232} Published response rates have ranged from 54% to 75% with 15% to 25% of patients achieving complete response.²²⁴⁻²²⁹ However, some investigators believe that overall response rates may be significantly lower.²²⁴ The best

responses are in erythrodermic patients. Complications of photopheresis are minimal because the treatments are performed *ex vivo*. Some patients may have nausea or an accentuation of erythema. About 10% may experience a transient fever after reinfusion of cells.²²⁵ Less frequently, hypovolemic hypotension and transient elevation of liver enzymes can occur.²²⁵

The mechanism of action of photopheresis is not well understood. Malignant lymphocytes may be directly killed by this approach. In addition, it has been postulated that photopheresis may induce cytokine production.²⁷⁹ Alternatively, there is some evidence that when the modified photoirradiated cells are reintroduced to the patients, they stimulate an immune reaction against the malignant clone of T cells, which results in an improved ability of the host immune system to respond to tumor cells.^{225,280-282}

Total Skin Electron Beam Radiation (TSEB)

The cells of CTCL are radiosensitive. The ability to treat the entire skin easily was dependent on the development of electron beam therapy and the concept of TSEB therapy for management of extensive MF was first described by Trump et al.²⁸³ In this modality, linear accelerator-generated electron beams are scattered by a penetrating plate, reducing the energy of the electrons. Electrons are therefore delivered to a limited depth (several millimeters to 1 cm) of the entire skin surface, thereby preventing systemic toxicity. The treatment generally involves a total dose of 3,000 to 3,600 centigray (cGy) given in an 8- to 10-week period.

The efficacy of TSEB has been shown in several studies.^{107,233-235} An update of a large series including patients with limited and generalized plaques, tumors, and erythroderma showed complete response rates of 98%, 71%, 36%, and 64%, respectively.²³⁴ Although many patients eventually relapse, about 50% of individuals with limited plaques and 20% of individuals with generalized plaques have long-term (>3 years) remissions.²³⁴ In patients with more advanced disease, electron beam can be helpful as palliation. Most patients receive only a single course of TSEB. However, Becker et al²³⁶ have shown that a second course at reduced dose produced six CRs and nine PRs among 15 relapsed patients treated, with good tolerance.

To decrease the incidence of relapse, some centers recommend adjuvant topical treatment (nitrogen mustard or PUVA) after completion of TSEB.^{107,234} Wilson et al²⁸⁴ recently suggested a survival benefit for advanced CTCL patients who are TSEB complete responders who receive adjuvant extracorporeal photochemotherapy.

Toxicity of electron beam radiation includes scaling, dryness, erythema, telangiectasia, eczema of the extremities, pigmentary changes, and sometimes irreversible hair or sweat gland loss. Careful radiation dosimetric techniques are required to adequately treat the skin without toxicity to normal tissues.

Single-Agent Chemotherapy

Many active agents (>20% response rate), including alkylating agents, antimetabolites, antitumor antibodies, vinca

alkaloids, topoisomerase-II inhibitors, and corticosteroids, exist in MF. In an extensive summary of the literature, Bunn et al²²⁴ showed that among 528 patients reported in single-agent chemotherapy trials, the CR rate was 32%. Median duration of response ranged from 3 to 22 months. In general, however, patients are not cured by this approach.²²⁴

The most data reported with single agents was with methotrexate, which had comparative activity at high doses (with leukovorin rescue) and at lower doses. This drug may be effective even in advanced disease. A recent study²⁹⁵ with low-dose methotrexate (5 to 125 mg, once weekly, by the oral, subcutaneous, or intramuscular route) showed a 58% response rate (CRs = 41%; PRs = 17%) among 29 patients with erythrodermic disease. Their median time to treatment failure was 31 months and median survival was 8.4 years.

Combination Chemotherapy

Combination chemotherapy given alone or combination chemotherapy administered with TSEB or nitrogen mustard was evaluated in large series of patients and summarized in a recent review.²²⁴ The response rate in a total of 331 patients was 81% and CR rate was 38%; duration of remission ranged from 5 to 41 months. Most of the 331 patients reported above had advanced disease. Hallahan et al²³⁷ reported the results of 10 years of follow-up in 21 patients with tumor-stage CTCL who were treated with TSEB followed by 6 months of combination chemotherapy. The CR rate was 52% with a median disease-free survival of 12 months. All patients had relapsed within 24 months. A randomized prospective clinical trial performed by Kaye et al²³⁸ evaluated aggressive treatment (TSEB combined with systemic chemotherapy) versus conservative management as initial treatment for CTCL. The chemotherapy consisted of cyclophosphamide, doxorubicin, etoposide, and vincristine; the conservative topical regimen was nitrogen mustard or PUVA. The response rate was 90% compared with 65% and the CR rate was 38% compared with 18%. However, there was no statistically significant difference in survival.²³⁸ Recently we²³⁹ have reported the results of a combined modality program using IFN- α plus *cis*-retinoic acid for 4 months, followed by combination chemotherapy, followed by TSEB, in patients with stage III or IV disease. Maintenance therapy with IFN- α and topical nitrogen mustard was given. The chemotherapy consisted of cyclophosphamide, methotrexate, etoposide, and decadron alternating with adriamycin, bleomycin, and vinblastine. In stage I and II disease, the same combined modality approach was taken but without the chemotherapy. In the 28 patients with stage I-IV disease treated, the response rate was 82% (CR rate, 71%). The median failure-free survival was 8 months, with most relapses occurring in patients with stage III or IV disease. However, 2 of the 11 patients with stage III or IV disease remain disease-free at 39+ and 46+ months.

Bone Marrow Transplant

Few patients with MF/SS have received transplants. Sterling et al²⁴¹ treated an erythrodermic patient with total body irradiation and autologous bone marrow transplant, and

achieved a short-lived response. Bigler et al²⁴⁰ used very high-dose combination chemotherapy with or without irradiation followed by autologous bone marrow transplant in 6 patients with advanced-stage MF. They reported that 5 of 6 patients achieved CRs. Although 3 of the responses lasted less than 3 months, 2 patients were still disease-free after 1 year.

To our knowledge, a series of MF/SS patients undergoing allogeneic bone marrow transplant has not been reported. However, this modality may be theoretically worthwhile because a graft-versus-leukemia/lymphoma effect is known to accompany graft-versus-host disease. The latter occurs predominantly in the skin, which is also the predominant site of involvement in MF.

Adenosine Analogues

Adenosine analogues include 2-deoxycoformycin (DCF), fludarabine, and 2-chlorodeoxyadenosine (2CDA). Adenosine deaminase deficiency is toxic to T cells and CTCLs have a low-growth fraction that appears sensitive to 2CDA *in vitro*.^{245,285} These observations, as well as the profound CD4 suppression that occurs after administration of these agents, prompted investigation of the adenosine analogues in T-cell lymphomas.

In a pilot study,²⁴⁵ a response rate of 47% using 2CDA as a single agent was reported. Kuzel et al,²⁴⁶ in their study with 2CDA, reported a 28% response rate. In our study²⁴⁷ the response rate was only 13%, and prolonged cytopenias after repeated dosing appeared to limit the usefulness of this drug. All these studies included small numbers (8 to 15) of patients. Mercieca et al²⁴² conducted a study which included 145 patients with T-cell malignancies treated with DCF. The overall response rate was 32%; the best responses were noted in patients with SS (62%), with CRs in 3 of 16 SS patients. Cummings et al²⁴³ reported a 50% remission rate with DCF in CTCL, but no information was given as to the exact disease subtype and whether SS cases were included. Another report also show high activity of DCF in MF when higher than standard doses were used.²⁴⁴ These results suggest that further investigation of DCF is warranted, especially in SS. In a study using fludarabine in 33 patients with MF the response rate was 19%; 1 patient had a CR and 5 patients had a PR. Duration of response was not reported in this study.²⁴⁸ DCF and fludarabine both have been used in combination with IFN- α with reported response rates of 41% and 51%, respectively (CR rate = 5% and 8%).^{257,258}

Cyclosporine

Cyclosporine inhibits proliferation of T cells. However, in reported studies, only 32% of the CTCL patients treated with cyclosporine had a PR; no CRs were seen. Toxicity was significant and included immunosuppression, infection, and renal insufficiency.²⁴⁹⁻²⁵³

IFNs

The mechanism of action of IFNs appears to be complex. IFN- α most likely acts upon the proliferation of keratinocytes and has an immunomodulatory effect, especially on macrophages and natural killer cells.^{286,287}

Both intralesional and systemic IFN have been used in the treatment of MF/SS. Vonderheid et al²⁵⁴ reported the results of a study including patients with early-stage disease; participants were treated with intralesional therapy with α -2B IFN. Ten of the 12 IFN-treated lesions regressed completely. The use of systemic IFN for CTCL was first reported by Bunn et al.²⁵⁵ IFN- α -2a was given to 20 patients; the response rate was 45% with 15% CRs.²⁵⁵ The literature summary²²⁴ shows that the overall response rate for IFN- α is 52%, with 17% CRs. The median duration of response is 4 to 28 months. These studies show that IFNs are active agents and produce responses in about half of patients. The clinical stage of disease appears to predict for response, with lower response rates in advanced stages.²⁹⁶ The responses develop slowly, over weeks to months. They generally last less than a year. There is no optimal recommended dose for IFN- α but many investigators²⁹⁶ suggest a low dose (3 million units administered three times per week²²⁴) because a dose/response has not been shown.

Studies have evaluated combinations of IFN- α with adenosine analogues, retinoids, or PUVA. Some of these studies suggest that combination therapy may increase the response rates although, again, a randomized study has not been done.²²⁴ (These studies are discussed in more detail in the sections on PUVA, adenosine analogues, and retinoids.)

Retinoids

Retinoids are vitamin A analogues, with a complex mechanism of action. They appear to act primarily on the differentiation and proliferation of epithelial cells, but also could have an immunoregulatory effect on the mononuclear infiltrate in the skin.²⁸⁸

Several studies have been conducted to evaluate responses of patients with MF/SS treated with retinoids.²²⁴ Single-agent acotinoid-ethylester, 13 *cis*-retinoid acid, and etretinate were administered in 120 patients. The overall response rate was 58%, with a CR rate of 19%. The median duration of response ranged from 3 to 13 months. Retinoids are generally well tolerated. Common side effects include dry skin and mucous membranes, hypertriglyceridemia, and increased liver function tests.

Because of the lack of overlapping side effects, retinoids have been combined with chemotherapy, radiation, and IFN- α , albeit in nonrandomized trials. Response rates and duration appear similar to those of each of the above modalities alone.^{224,289,290}

ILs

IL-2 is a lymphokine that promotes T-cell activation and proliferation. It has been used in cancer therapy and is presumed to act by stimulating the immune system with enhancement of both CD8⁺ and natural killer cytotoxic activities and by induction of lymphokine-activated killer cells. However, because CTCL is a T-cell disease, theoretically it should be detrimental to patients with MF/SS. Nevertheless, a partial response was obtained in a case of CTCL treated with intralesional injection of IL-2.²⁹¹ Rybojad et al²⁹² reported a case of complete clinical remission of resistant

CTCL with systemic IL-2 treatment. Finally, Marolleau et al²⁷⁰ achieved responses in 5 of 7 patients (3 CRs and 2 PRs). The CRs are ongoing at 6, 28, and 33 months. These results suggest that further trials may be indicated.

Some investigators⁴⁸ have shown that IL-12 as well as IFN- γ and IL-2 production by peripheral blood mononuclear cells in SS is deficient, whereas IL-4 is increased. After exposure to IL-12, these cytokine abnormalities normalize, and natural killer cell activity is increased. However, to date IL-12 has not been reported in the clinical treatment of MF.

IL-2 Fusion Toxin

Expression of IL-2 receptors on the malignant cell in MF/SS varies. Because about half of the patients express significant numbers of receptors,²⁷³ one strategy would be to target these receptors. Therefore, an IL-2 fusion toxin that binds to high-affinity IL-2 receptor has been investigated. The IL-2 fusion toxin is a genetically engineered molecule that is a hybrid of IL-2 and diphtheria toxin.^{271,274,293} Phase II trials²⁷⁴ with an IL-2 fusion toxin (DAB₄₈₆IL-2 containing 486 amino acids of the diphtheria toxin fused to IL-2) reported response rates of 21% (in 29 patients). Patients whose malignant cells lacked IL-2 receptors did not respond to treatment. Although some patients develop antibodies, this did not preclude a response.²⁷¹ DAB₃₈₉IL-2 is a similar recombinant fusion toxin with greater binding affinity to the IL-2 receptor. A response rate of 45% with a CR rate of 9% (1 patient had a CR) was reported in 11 patients treated in phase I-II studies.²⁷³ In a recent multi-institution trial of DAB₃₈₉IL-2, 35 IL-2-expressing MF patients were treated. Thirteen had a response and the median response duration was 4.7 months.²⁷² Based on these studies, phase III trials have been initiated.

Monoclonal Antibodies

Monoclonal antibodies either alone^{259,260} or conjugated to radioisotopes^{261,262} or toxins²⁶³ which react with cell surface antigens of T cells (such as CD4 or CD5) have been used in a small number of patients with CTCL.^{259,260,264-266} Objective responses have been noted in only a few individuals and were short-lived.^{224,264} However, regression of skin and LNs and a reduction of the number of malignant circulating cells have been documented. Taken together, the studies²⁵⁹⁻²⁶⁹ suggest that antibody which is radiolabeled or conjugated with a toxin may be preferable to naked antibody.

SUMMARY AND PERSPECTIVE

MF and SS represent a spectrum of low-grade cutaneous T-cell lymphomas characterized by infiltration of the skin by malignant mature T lymphocytes, almost always of the T-helper subset. In its early stages, however, both the clinical and histologic features of MF may be nonspecific, making the disease particularly difficult to diagnose. The issue is further complicated by the variety of "benign" cutaneous conditions that can mimic MF at both the clinical and microscopic level (Table 4).

MF typically evolves from the early patch/plaque stage to the eventual development of tumors, as well as nodal and

visceral involvement. Alternatively, diffuse erythroderma, which is almost invariably accompanied by blood involvement, may develop and is known as Sézary syndrome. Interestingly, in patients with SS, the bone marrow exam generally shows significantly less involvement by lymphoma than the peripheral blood. Recent studies based on cytokine profiles have suggested that the Th1 subset of T-helper cells is involved in MF whereas the Th2 subset has been implicated in SS,⁸⁹ a finding that may explain the distinct evolution of the disease to tumor stage in some patients and to erythroderma in others (although it is not clear if the Th1 cells in MF represent the malignant T cells or immunoregulatory reactive T cells). Large cell transformation may occur, especially in patients with tumor-stage disease, and is associated with a worse prognosis.¹⁸⁹⁻¹⁹² Although MF is considered an indolent lymphoma, survival is highly influenced by stage. Specific prognostic features for MF/SS are not as well defined as in other lymphomas.

As with many indolent lymphomas, a wide variety of therapies can produce responses in MF/SS, but are generally not curative. However, therapy of MF is unique among lymphomas because of the efficacy of skin-directed modalities. In the early stages of disease, topical nitrogen mustard, PUVA, or total skin electron beam is often used. Multiple single-agent and combination chemotherapies have been tried for all stages of MF and for SS, but perhaps the most data exist for methotrexate. Currently, it is not clear that combination therapy is superior to single agents (Table 7). Furthermore, although aggressive initial management of MF with chemotherapy and radiation may produce a trend toward higher response rates than conservative, skin-directed management, a randomized trial has not shown a statistically significant difference,²³⁸ nor has a survival advantage been demonstrated. Bioimmunotherapy has also been used with some success (Table 7). IFN- α and retinoids produce responses in over half of patients. Surprisingly, IL-2 (a T-cell growth factor) has also been reported to have activity, although only a small number of patients have been treated.²⁷⁰ In addition, about half of MF/SS patients express significant levels of IL-2 receptors on their malignant cells. Therefore, a genetically engineered IL-2 molecule conjugated to a diphtheria toxin which would target these cells is in clinical trials. Combining certain modalities, ie, IFN- α together with PUVA, has been reported to have high (90%) response rates.²⁵⁶ Allogeneic bone marrow transplantation has generally not been performed, although theoretically this modality may be of interest especially because it is conceivable that a graft-versus-lymphoma effect concentrated in the skin might be produced. Some therapies such as extracorporeal photopheresis or the adenosine deaminase inhibitor DCF may be more effective in patients with erythrodermic disease than in patients with tumors.^{224-232,242} Importantly, one of the most common causes of death is infection, especially due to staphylococcal organisms. Therefore, patients presenting with fever and/or chills should be aggressively cultured and treated with appropriate antibiotics.

The etiology of MF/SS remains unclear. Etiologic/pathogenic factors which have been implicated include viruses, various oncogenes, and cytokines, environmental toxins,

bacterial (staphylococcal) superantigens, and altered expression of adhesion molecules (Table 1 through 3). Perhaps the strongest evidence relates to the presence of a defective or variant HTLV-1 because polymerase chain reaction-based studies by some (but not all) investigators suggest that over 90% of patients harbor HTLV-1 pol and/or tax sequences, even though the vast majority of these individuals test negative for antibodies to HTLV-1.^{7,16-20} Finally, MF represents a disease with fairly well-delineated stages of clinical progression and is easily managed during its early phases. Therefore, future studies should also be aimed at elucidating the molecular and biologic changes driving evolution.

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