



Alexey Bobylev. *Country Fishermen*, 2003. Oil on canvas, 70 × 80 cm. Courtesy of the St. Petersburg Art Salon, Russia.

*A multidisciplinary approach  
in diagnosing, staging, and  
treating mycosis fungoides  
improves the outlook of  
patients with this disease.*

# The Diagnosis, Staging, and Treatment Options for Mycosis Fungoides

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**Background:** *Cutaneous T-cell lymphoma (CTCL) represents a spectrum of diseases composed of malignant T lymphocytes. The most common type is mycosis fungoides (MF). An accurate diagnosis of early MF may be difficult because of the varied clinical and histologic expressions of the disease.*

**Methods:** *The authors review the epidemiology, possible risk factors, clinical manifestations, diagnostic techniques, staging, prognosis, and treatment options for MF.*

**Results:** *The varied and often nonspecific clinical and histologic presentations of MF may delay diagnosis and staging, thus necessitating further studies such as immunophenotyping and T-cell receptor gene rearrangement analysis.*

**Conclusions:** *A multidisciplinary approach to the diagnosis, staging, and treatment of MF assists in optimizing outcomes from management of patients with this disease.*

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*Submitted September 11, 2006; accepted January 11, 2007.*

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*No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.*

*The editor of Cancer Control, John Horton, MB, ChB, FACP, has nothing to disclose.*

**Abbreviations used in this paper:** CTCL = cutaneous T-cell lymphoma, MF = mycosis fungoides, PUVA = psoralen and ultraviolet A.

## Introduction

Cutaneous T-cell lymphoma (CTCL) is generally classified as a type of non-Hodgkin's lymphoma. CTCL consists of a heterogeneous group of lymphoproliferative disorders that primarily present in the skin and are composed of malignant clonal T lymphocytes. Indolent subtypes include mycosis fungoides (MF) and its variants, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma. Aggressive subtypes include Sézary syndrome, primary cutaneous natural killer (NK)/T-cell lymphoma nasal-

type, primary cutaneous aggressive CD8+ T-cell lymphoma, primary cutaneous  $\gamma/\delta$  T-cell lymphoma, and primary cutaneous T-cell lymphoma, unspecified.<sup>1</sup> More than 65% of cutaneous lymphomas are T-cell disorders.<sup>1</sup> B-cell lymphomas account for approximately 25% of cases, and up to 10% of cases are unspecified. MF is the most common subtype of CTCL, accounting for almost 50% of all primary cutaneous lymphomas. Accurate diagnosis of early CTCL is difficult because of the varied clinical and histologic expressions of the disease and also because of a lack of uniformity in diagnosis and treatment.

Issues in CTCL, including epidemiology, possible risk factors, clinical manifestations, diagnosis, staging, and treatment, are summarized in this publication, with a focus on MF, as well as a special emphasis on a multidisciplinary approach in management based on staging information. Several in-depth reviews have been recently published regarding the diagnosis and treatment of MF.<sup>2-6</sup>

## Epidemiology

The most common type of CTCL is MF, which is approximately twice as common in men as in women, while blacks have twice the incidence of whites.<sup>7-12</sup> It is less common in Asians and Hispanics.<sup>13</sup> Most cases are diagnosed in the fifth and sixth decades (median age 55 to 60 years). Children and adolescents are rarely affected. Approximately 1,000 new cases are diagnosed each year in the United States.<sup>12</sup> The course of MF is usually indolent, with slow progression over years to decades, but it can be unpredictable. It usually demonstrates epidermotropism by involving the skin first but, with time, it can spread to lymph nodes, blood, and viscera. Survival ranges from only a few months to several decades, depending on the stage of the disease. Most patients experience a prolonged survival with little morbidity, while some patients develop a fulminant course with rapid dissemination and death. A diagnosis of MF is often delayed for many years as it can masquerade clinically as other entities such as dermatitis or fungal infection.

## Etiology

The term *mycosis fungoides* was initially used by Alibert in 1832 after his description in 1806.<sup>13</sup> He described an unusual skin eruption that developed into tumors shaped like mushrooms. It became understood that MF was a misnomer since there is no association with a fungus, and MF was rather a cutaneous manifestation of lymphoma.

The etiology of MF is unknown. Several theories on the etiology of MF have been postulated, including expo-

sure to environmental, genetic, and infectious agents. Early epidemiologic studies suggesting a causative role of environmental exposure to chronic antigenic stimulation (eg, industrial chemicals, metals, and herbicides/pesticides) have not been substantiated by subsequent studies.<sup>14-18</sup> The prevailing theory is that MF likely develops secondary to chronic antigenic stimulation due to a multitude of factors in a stepwise process involving mutations in oncogenes and certain DNA repair genes. A number of infectious agents have been investigated, including human T-cell lymphotropic virus (HTLV) I/II, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human simplex virus (HSV).<sup>17,19-23</sup>

At the forefront of etiologic research has been the hypothesis of a retroviral cause of MF. HTLV-I has a causal relation to adult T-cell leukemia/lymphoma. However, most MF patients are negative for the virus, and the known HTLV-I epidemiologic patterns have not been observed in MF. Nevertheless, HTLV-I-like retroviral particles have been found in cultured immortalized mycosis cells, and HTLV sequences have been identified by Southern blotting and polymerase chain reaction (PCR) in affected patients. Thus, the role of retroviruses in MF remains uncertain.<sup>14-26</sup> Perhaps HTLV-I plays a role in only a subset of MF cases.

Some groups have found serologic evidence of the Epstein-Barr virus in MF patients, suggesting a possible role in the pathogenesis, although it may be simply a bystander virus.<sup>27,28</sup> One report noted that 97% of patients with late-stage MF or Sézary syndrome are seropositive for CMV compared with 57% of healthy bone marrow donors.<sup>29</sup> Other implicated risk factors include genetic predisposition, radiation exposure, and preexisting malignancies, although there are little supporting data.<sup>30</sup> Some evidence suggests immunosuppression as a risk factor for MF, including cases of documented MF arising in patients infected with HIV,<sup>31</sup> in organ transplant patients,<sup>32</sup> and in patients treated for lymphoma.<sup>33</sup> Staphylococcal superantigens, persistent Chlamydia infection, and defective T-cell apoptosis have also been postulated.<sup>34-36</sup>

## Clinical Manifestations

Three classical cutaneous phases of MF — patches, infiltrated plaques, and tumors — were described by Bazin<sup>37</sup> in 1876. The disease may progress through each of these phases, which frequently overlap or occur simultaneously. If only tumors are present, without prior or coexisting patches or plaques, the diagnosis of MF should be questioned.<sup>1-6</sup> In the past, MF has been reported as presenting with tumor nodules as the initial disease presentation without evolution, originally termed the *d'emblee* variant by Videl and Brocq<sup>38</sup> in



Fig 1. — Patch-stage MF. Early skin lesions may mimic eczema or papulosquamous eruptions such as tinea corporis, secondary syphilis, or psoriasis.

1885. In retrospect, the majority or all of these cases would now be classified as high-grade cutaneous pleomorphic lymphoma or other variants of T-cell lymphoma.<sup>39,40,41</sup> In addition to the classical (Alibert) form, patients may present with a poikilodermatous variant (see below), with large-plaque parapsoriasis, or with erythroderma (not to be confused with Sézary syndrome with leukemic manifestations). Other rare presentations include bullous, follicular, hyperpigmented, hypopigmented, verrucous/hyperkeratotic, pustular, lichenoid papular, palmoplantar psoriasiform, granulomatous, and acanthosis nigricans-like variants.<sup>1,6,42</sup> Variants with distinctive clinicopathologic features include folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin; these variants are discussed below. The World Health Organization/European Organization for Research and Treatment of Cancer (WHO/EORTC) panel, composed of a group of dermatologists and pathologists expert in cutaneous lymphomas, have developed a consensus classification of MF in the context of other cutaneous lymphomas.<sup>1,5</sup>

Early skin lesions may mimic eczema or papulosquamous eruptions such as tinea corporis, secondary syphilis, or psoriasis (Fig 1). Most investigators believe that large-plaque parapsoriasis represents an early form of MF.<sup>43-45</sup> Sequential biopsies of such lesions may be necessary to establish or confirm a diagnosis of MF.



Fig 2. — Poikilodermatous variant of MF. Patch lesions have cigarette-paper-like atrophy, telangiectasia, and mottled hyperpigmentation.



Fig 3. — Plaques of MF on an extremity. Plaques of MF are elevated due to epidermal hyperplasia or significant neoplastic lymphocytic infiltrates.

Patch-stage lesions are erythematous patches or slightly raised plaques with a fine scale.<sup>46</sup> The lesions may be single or multiple and are often located on the buttocks, thighs, and abdomen. Patch lesions may be intensely pruritic or entirely asymptomatic. *Poikiloderma atrophicum vasculare* is a term used to describe patch lesions with cigarette-paper-like atrophy, telangiectasia, and mottled hyperpigmentation (Fig 2).

Plaques of MF are elevated due to epidermal hyperplasia or significant neoplastic lymphocytic infiltrates (Fig 3). These lesions may develop from preexisting patches or de novo. They are usually red-brown and sharply demarcated, but they may coalesce to form annular, arciform, or serpiginous patterns, sometimes with central clearing. Infiltrative plaques occurring on the face may result in leonine facies, and those appearing in hairy areas may produce alopecia or cysts. Erythroderma (exfoliative dermatitis) may occur as a result of diffuse infiltration of the skin by neoplastic cells with or without scale.

The lesions of tumor-stage MF are typically violaceous, exophytic, mushroom-shaped tumors that preferentially affect the face and body folds (Fig 4).<sup>46</sup> Lesions often undergo ulceration or necrosis and secondary infection. Pruritus may decrease in intensity during this stage. Over 50% of deaths from MF are

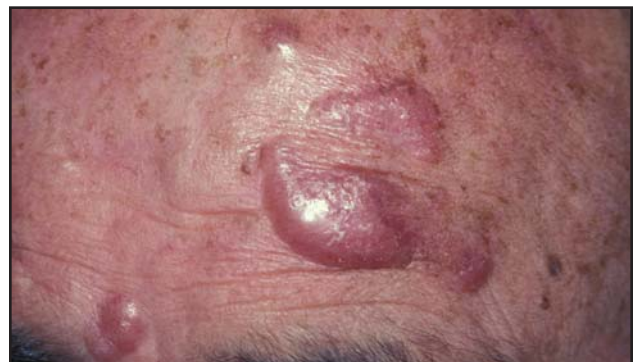


Fig 4. — Tumor-stage MF. Lesions are typically violaceous, exophytic, mushroom-shaped tumors that preferentially affect the face and body folds.

caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa* sepsis. Tumors may undergo transformation into a CD30+ (Ki-1+) large-cell anaplastic variant of CTCL with an aggressive biological behavior. Transformation has been reported to range between 8% and 55% of tumor-stage MF.<sup>47-49</sup> In contrast to the primary CD30+ anaplastic large-cell lymphomas that generally have a good prognosis, the prognosis for secondary CD30+ lymphomas developing in association with MF is poor, with median survival from transformation ranging from 11 to 36 months.<sup>49-52</sup>

Folliculotropic MF shows preferential involvement of the head and neck area. Lesions may present as grouped follicular papules, acneiform lesions, and indurated plaques. They are often associated with alopecia, especially of the eyebrows and scalp (Fig 5).<sup>1-5, 53-56</sup> Lesions are often pruritic and sometimes burning. Patients are mostly men and often elderly.<sup>53</sup> Due to the depth of the associated infiltrate, treatment with topical agents and/or psoralen and ultraviolet A (PUVA) irradiation is often ineffective. Histologically, there is preferential infiltration of hair follicles with or without the presence of mucin.<sup>54-56</sup> The presence of mucinous degeneration of the hair follicles is termed *follicular mucinosis*.

Pagetoid reticulosis (Woringer-Kolopp type) typically presents as a single, erythematous lesion localized to the extremities. It expands gradually, often over many years, to form a thick plaque or localized group of plaques (Fig 6).<sup>57</sup> The clinical differential diagnosis



Fig 5. — Facial papules representing folliculotropic MF. Lesions may appear as grouped follicular papules, acneiform lesions, or indurated plaques.



Fig 6. — A solitary poikilodermatous patch of Pagetoid reticulosis. It typically presents as a single, erythematous lesion localized to the extremities.

includes Bowen's disease and superficial basal cell carcinoma. The disease usually involves men, with a predilection for the sixth and seventh decades. Extracutaneous dissemination and disease-related deaths have never been reported.<sup>1,5</sup> This entity is controversial, and some investigators believe Woringer-Kolopp disease is a benign lymphoproliferative process analogous to lymphomatoid papulosis, only occasionally terminating in MF, while most believe it to be a variant of MF.<sup>58</sup>

Granulomatous slack skin is an extremely rare entity typified by folds of lax or boggy, pendulous skin often localized to the flexural regions, especially the axillae and groins, with a histologic granulomatous infiltrate with clonal T cells.<sup>59</sup> There is a predilection for men in the third to fifth decades.<sup>60</sup> Patients are at risk of developing a second lymphoma, most often Hodgkin's lymphoma (one third of patients) or classical MF.<sup>59-61</sup> The clinical course is usually indolent.

Sézary syndrome accounts for approximately 5% of new cases of CTCL and represents the leukemic variant of CTCL. Sézary syndrome is recognized by the classic triad of generalized erythroderma, leukemia, and lymphadenopathy.<sup>62,63</sup> Malignant T cells with hyperconvoluted cerebriform nuclei circulate in the blood. Sézary cells can be detected in the peripheral blood in 90% of erythrodermic CTCL patients.<sup>64</sup>

The International Society of Cutaneous Lymphoma (ISCL) has recommended criteria for the diagnosis of Sézary syndrome. One or more of the following should be present: an absolute Sézary count of at least 1,000 cells/mm<sup>3</sup>, immunophenotypical abnormalities (a CD4: CD8 ratio of  $\geq 10$ ), loss of any or all of the T-cell antigens CD2, CD3, CD4, and/or CD5, and the demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods.<sup>65</sup> As the disease progresses, the ratio of CD4 (T helper) to CD8 (T suppressor) becomes elevated by an expansion of the malignant CD4 clonal population in Sézary syndrome, as well as a decrease in the normal CD4 and CD8 populations. Circulating Sézary cells have also been found in up to 20% of



Fig 7. — Sézary syndrome. Its major clinical manifestation is widespread pruritic erythroderma.

plaque or tumor-stage MF, as well as in several benign dermatologic conditions.<sup>66</sup> A CD4:CD8 ratio >5 and nuclear contour indexing using electron microscopy are more sensitive indicators of the quantity of circulating Sézary cells than light microscopy.<sup>67,68</sup> Despite the continued uncertainty over the extent of peripheral blood involvement, widespread pruritic erythroderma is the major clinical manifestation of Sézary syndrome (Fig 7). Patients may have fever, chills, weight loss, and malaise. Other features may include hepatomegaly, onychodystrophy, leonine facies, ectropion, alopecia, and palmoplantar keratoderma.<sup>69</sup>

## Diagnosis

The diagnosis of MF is usually made by recognition of the characteristic clinical manifestations of the disease plus routine histology. In difficult cases, a preliminary diagnosis may be supported by additional laboratory tests such as immunophenotyping, flow cytometry, and T-cell receptor gene rearrangement (TCRGR) analysis. Light microscopy of sections from involved skin stained with hematoxylin-eosin remains the diagnostic gold standard, but the diagnosis in early stages may be difficult because it initially may resemble other chronic inflammatory dermatoses.<sup>70</sup> Occasionally, sequential biopsies are necessary before the diagnosis is made. In the prototypical plaque stage, the histologic picture is often diagnostic. Histology reveals a band-like or lichenoid infiltrate of mononuclear cells within the papillary dermis with overlying epidermotropism (intraepidermal lymphocytes with a paucity of spongiosis). These lymphocytes may be found singly or in collections within the epidermis, often surrounded by a clear halo (Pautrier microabscesses). High-power examination of mononuclear cells reveals hyperchromatic and irregular nuclear contours (Fig 8). The epidermis frequently shows a pattern of psoriasiform epidermal hyperplasia with hyperkeratosis and focal parakeratosis.

Other reported histologic features include the presence of lymphocytes within the epidermis that are

larger than those within the dermis (present in approximately 20% of MF biopsies, and rare to absent in controls), basilar lymphocytes (lymphocytes aligned with the basal layer of the epidermis in a “string of pearls” pattern), “medium-large” hyperchromatic lymphocytes 7 to 9  $\mu\text{m}$  in diameter approximating the width of basilar keratinocytes, and papillary dermal fibrosis (thickened and wiry collagen bundles within the papillary dermis).<sup>71</sup>

TCRGR analysis, using Southern blot or PCR methods, helps to confirm early or atypical CTCL when the histology is suggestive but not diagnostic.<sup>72</sup> TCRGR analysis is well established as a determinant of clonality within lymphoid populations. The TCR is a glycoprotein with four subunits ( $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ). In normal peripheral blood T lymphocytes, the TCR genes are composed of 90% to 98%  $\alpha/\beta$  subunits. During the process of antigen recognition, the  $\beta$  subunit undergoes TCRGR and, as a result, each T cell produces a singly unique TCR gene. A polyclonal population of T cells produces a variety of TCR gene products. In contrast, the T-cell expansion population in CTCL is monoclonal as multiple copies of the same TCRGR are produced by identical daughter cells. The cells may be detected by Southern blot analysis (DNA hybridization) or PCR if found in large enough quantities.

Most reported cases of CTCL have a clonal rearrangement detected by TCRGR analysis. The diagnostic value of TCRGR analysis by Southern blot is limited by a low sensitivity since a level of abnormal T-cell clone infiltration below 5% may be too low for detection. PCR has a sensitivity that is at least a level of magnitude greater than Southern blotting, and the increase in the limit of detection may allow a diagnosis of CTCL in very early disease stages.<sup>73,74</sup>

The PCR method for detection of TCRGR is a promising diagnostic technique. Further advances in our knowledge of clonality in CTCL are necessary before PCR can be used as a sole diagnostic test for CTCL. For example, it is acknowledged that some nonneoplastic T-cell disorders such as pityriasis lichenoides et varioliformis acuta may display some level of clonality.<sup>72</sup>

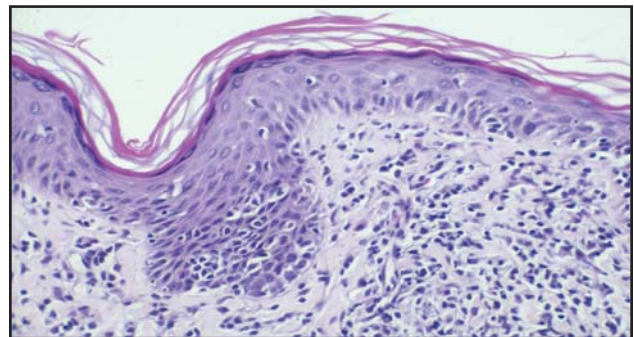


Fig 8. — Epidermotropism in patch-stage MF. The epidermis frequently shows a pattern of psoriasiform epidermal hyperplasia with hyperkeratosis and focal parakeratosis.

Further clinical evaluation of CTCL patients includes a complete history and physical examination, emphasizing the types of skin lesions, body surface area, lymph node, liver, and spleen involvement.<sup>1-5</sup> Baseline tests should include a complete blood cell count; additional tests that may be useful in staging patients with clinically advanced MF include peripheral blood flow cytometry for T-cell subsets, serum chemistries (liver and renal function tests, calcium, phosphorus, uric acid, lactate dehydrogenase), chest radiograph, and biopsy of palpable lymph nodes. Staging procedures for patients with advanced disease would also include computed tomography (CT) scan of the neck, abdomen, and pelvis, and also possibly bone marrow biopsy.

## Staging and Prognosis

A number of staging systems for MF have been proposed. The simplest and most widely used system, adopted by Bunn et al,<sup>75</sup> incorporates the tumor-node-metastasis (TNM) system. This staging system combines both clinical and histopathologic perspectives (Table), and a recent revision includes blood staging (TNMB).<sup>1,5</sup> An alternative system divides patients into three prognostic groups based on lymph node involvement at initial presentation<sup>76</sup>: (1) good-risk patients with patch or plaque skin lesions without lymph node, blood, or visceral involvement (median survival 12 years), (2) intermediate-risk patients with plaques, tumors, or erythroderma with lymph node and or blood involvement but no visceral disease (median survival 5 years), and (3) poor-risk patients with visceral involvement or complete lymph node effacement (median survival 2.5 years). Calculation of the tumor burden index (TBI) is useful and is obtained by multiplying the percentage of body surface area involved and weighted factors related to patches, plaques, and tumors. The product of the formula ranges between 1 and 6.3, the highest figure representing extensive disease with one or more tumors.<sup>77</sup>

A lymph node grading system in MF patients proposed by Sausville et al<sup>78</sup> has been used to define prognosis once the diagnosis of MF has been established in the skin. In this system, LN1 nodes have single infrequent atypical lymphocytes in paracortical T-cell regions, LN2 nodes have small clusters of paracortical atypical cells, LN3 nodes have large clusters of atypical cells, and LN4 nodes are partially or totally effaced by atypical cells. The LN classification directly correlates with disease progression as well as with survival and prognosis. It must be emphasized, however, that the current recommendation is that biopsy of only enlarged LNs is undertaken in the staging of MF patients. Bone marrow biopsies are necessary only in

staging patients with advanced MF and should not be routinely undertaken in low-grade disease.

Standard treatment regimens in MF include skin-directed therapies such as PUVA, topical chemotherapy with mechlorethamine (nitrogen mustard), topical retinoids (bexarotene gel), and total skin electron-beam (TSEB) radiation. In patients with more extensive disease, treatment includes systemic therapies such as chemotherapy, photopheresis, oral retinoids (bexarotene), and interferon. A stage-adapted approach to CTCL therapy is used most often.<sup>79</sup> The various treatment modalities have been reviewed in depth elsewhere<sup>2,3,5</sup> but are summarized in brief below.

Currently, a conservative approach using skin-directed therapy is the preferred first-line treatment for early-stage MF. This includes topical agents such as corticosteroids, phototherapy (broad or narrowband ultraviolet B [UVB], PUVA), cytostatics, and biologics.<sup>80</sup> Studies have failed to show an additional survival benefit in

**Table. — Staging of Cutaneous T-Cell Lymphoma: TNMB Classification**

Classification	Description		
<b>T: Skin</b>			
T0	Lesions clinically and/or histopathologically suggestive of CTCL		
T1	Limited plaques, papules, or eczematous patches covering <10% of skin surface		
T2	Generalized plaques, papules, or erythematous patches covering ≥10% of skin surface		
T3	Cutaneous tumors		
T4	Generalized erythroderma		
<b>N: Lymph Nodes</b>			
N0	No palpable lymphadenopathy, lymph node pathology negative for CTCL		
N1	Palpable lymphadenopathy; lymph node pathology negative for CTCL		
N2	No palpable lymphadenopathy, lymph node pathology positive for CTCL		
N3	Palpable lymphadenopathy, lymph node pathology positive for CTCL		
<b>M: Viscera</b>			
M0	No visceral organ involvement		
M1	Visceral organ involvement, pathology present		
<b>B: Blood</b>			
B0	Atypical circulating cells not present (<5%)		
B1	Atypical circulating cells present (≥5%)		
<b>Stage</b>	<b>T</b> <b>N</b> <b>M</b>		
IA	1	0	0
IB	2	0	0
IIA	1–2	1	0
IIB	3	0–1	0
III	4	0–1	0
IVA	1–4	2–3	0
IVB	1–4	0–3	1

Adapted from Bunn PA Jr, Lamberg SI. Report of the Committee on Staging and Classification of Cutaneous T-cell Lymphomas. *Cancer Treat Rep.* 1979;63:725-728.

patients with MF by using aggressive modalities including combination chemotherapy and radiotherapy.<sup>81</sup> For minimally perceptible lesions that are clinically and/or histopathologically suggestive of CTCL (stage 0), corticosteroids are indicated, and class III corticosteroids have been shown to induce clinical remission in a significant percentage of early-stage MF (stage IA-B).<sup>82</sup>

Topical nitrogen mustard (mechlorethamine, HN2) is an alternative topical therapy for minimal disease burden and sites that are unresponsive or difficult to reach with PUVA. HN2 induces a complete remission rate of approximately 30% to 60%, with better results in early rather than advanced disease.<sup>83</sup> HN2 can be applied as an aqueous solution that is prepared by dissolving the contents of a 10-mg vial in 50 mL of water, or it can be compounded as an ointment. Side effects of HN2 include allergic and irritant contact dermatitis, pruritus, and hyperpigmentation.<sup>83</sup> Hypersensitivity reactions to the topical solution may develop in 35% to 58% of patients.<sup>83,84</sup> An immediate-type hypersensitivity reaction with urticaria can also occur in up to 8% of patients.<sup>85</sup> Unlike delayed hypersensitivity reactions where desensitization may result, immediate hypersensitivity reactions can produce potentially life-threatening anaphylactic reactions and would result in discontinuation of the medication. Ointment-based HN2 has been used since 1982, and the response, survival, and relapse rates are similar, but the incidence of hypersensitivity reaction is significantly less than with the solution.<sup>86,87</sup> In addition, the ointment remains stable for at least 40 days at 37°C and 80 days when refrigerated at 4°C. In contrast, the same concentration of aqueous solution is fully degraded after only 4 days.<sup>88</sup> Topical carmustine (BCNU) has similar efficacy and produces fewer hypersensitivity reactions.<sup>89</sup>

Topical therapy with imiquimod, a toll-like receptor-binding immune response modifier, has been reported to be beneficial for some patients with localized stage IA MF. It is unlikely a consideration for patients with widespread disease due to its toxicity and cost.<sup>90</sup>

Treatment of MF by PUVA was described by Gilcrest et al<sup>91</sup> in 1976 and is considered an acceptable first-line treatment for stage I through IIA disease. It is a skin-directed therapy that simultaneously targets both malignant T cells and Langerhans cells. PUVA is effective in clearing early-stage MF and in prolonging remission with maintenance therapy.<sup>92-94</sup> In a study of 82 patients with a mean follow-up of 45 months,<sup>95</sup> complete clearing of lesions was shown in 88% with limited plaque disease and in 51.9% with extensive plaque disease. The mean duration of remission was 13 months for patients with limited plaque disease and 11 months for patients with extensive plaque disease. Broadband UVB produces response rates as high as 74% in stage I patients with a median time to remission of 5 months.<sup>79</sup> Narrowband UVB has been shown to be a

useful alternative to PUVA and is effective without the need for oral psoralen. UVA is generally well tolerated but may not penetrate deeply enough to be effective in patients with tumor-stage disease. In patients with an inadequate response to PUVA, combination therapy with retinoids-PUVA or interferon (IFN)-PUVA should be considered.<sup>96-98</sup> Side effects include erythema, nausea due to oral psoralen, pruritus in 10% to 20% of patients, and photocarcinogenesis.

MF is extremely radiosensitive and is perhaps the most effective single skin-direct therapy for MF.<sup>99</sup> Thick or eroded plaques and tumors respond to low doses (4 Gy at 80 to 120 kV). TSEB therapy may be instituted in patients with widespread disease. An 84% complete response rate and a 10-year survival rate of 46% have been reported.<sup>100</sup> Relative response rates of 96% to 100% are achieved in stage IA/B disease and approximately 36% in stage IIB disease. However, because of the high rate of relapse with TSEB therapy, adjuvant therapy might include HN2 (to prolong remission) or PUVA either given alone or combined with oral bexarotene or interferon- $\alpha$ .<sup>100-102</sup> Side effects associated with radiation therapy include xerosis, erythema, telangiectasia, extremity edema, and alopecia.<sup>102</sup>

The treatment of choice for patients with erythrodermic disease (stage III) is extracorporeal photopheresis (ECP), which was first described as a treatment for CTCL by Edelson et al<sup>103</sup> in 1987. ECP involves the removal of leukocytes by leukapheresis after ingestion of or exposure to 8-methoxypsoralen (8-MOP). The ex vivo cells are exposed to UV light and then reinfused into the patient. Although the exact mechanism is not fully elucidated, the resultant alterations of cell-surface antigens induce apoptosis and are thought to alter the function and differentiation of dendritic cells. The majority of patients show complete clearance or >50% improvement with therapy and a prolonged survival compared with historical control groups.<sup>104-106</sup> However, ECP has been shown to be less effective in patients with a T-cell clone in the peripheral blood. The poor responders have more advanced disease with elevated CD4/CD8 ratios. ECP can be used in combination with TSEB and other modalities to produce and maintain remission.<sup>106</sup>

In addition, for stage III disease, immunotherapy with low-dose IFN- $\alpha$  may be added if the response to photopheresis is incomplete.<sup>107</sup> The three classes of IFN ( $\alpha$ ,  $\beta$  and  $\gamma$ ) exhibit antiviral, antiproliferative, and immunomodulatory effects.<sup>108</sup> The most commonly used IFN for the treatment of CTCL is IFN- $\alpha$ , subtype 2a. The first use of systemic IFN- $\alpha$  for CTCL was first reported by Foon and Bunn in 1986.<sup>109</sup> The optimal dose of IFN has yet to be determined. Kohn et al<sup>110</sup> studied the use of intermittent high-dose IFN- $\alpha$ 2a therapy in 24 patients with advanced CTCL who had failed at least one previous treatment. Complete response was seen in 4% of patients and a partial response was

achieved in 25% of patients. Side effects of IFN- $\alpha$ 2a include fever, chills, lethargy, hepatotoxicity, leukopenia, and a reversible nephrotic syndrome.<sup>111</sup>

Bexarotene, a novel retinoid with a high affinity to the retinoid X receptor, was approved by the US Food and Drug Administration (FDA) in 1999 for treatment of patients with refractory MF.<sup>112</sup> Monotherapy at a dose of 300 mg/m<sup>2</sup> per day was shown to produce response rates of 20% to 67% in a randomized open-label multicenter trial. It may be given in combination with PUVA at significantly lower doses of 150 to 300 mg/d in IA-IIB patients with reported high response rates. Blood lipids and serum thyroxine need to be monitored, especially in patients receiving higher doses. Bexarotene is also available in a 1% gel and has been shown to produce significant responses as a topical application in patient with early-stage MF.<sup>113</sup> The gel is tolerated well, but some local skin irritation has been reported with its use. Overall response rates of greater than 60% and a 21% complete response rate have been achieved.

Denileukin diftitox, a novel fusion toxin that consists of sequences of interleukin-2 (IL-2) and fragments of diphtheria toxin, has FDA approval for the treatment of MF and other lymphoid tumors expressing the high-affinity IL-2 receptor (CD25), including both T- and B-cell lymphomas.<sup>114</sup> Upon internalization, the toxic fragment of the chimeric protein terminates protein synthesis and promotes cellular apoptosis.<sup>115</sup> Retinoid X receptor (RXR) retinoids have been shown to upregulate the high-affinity IL-2 receptor in leukemic T cells<sup>116</sup> and enhance efficacy. Administration of denileukin diftitox is conducted at 3-week intervals and may be associated with infusion-related hypersensitivity reactions and a vascular leak syndrome.<sup>114</sup>

Chemotherapy for patients with refractory disease may be instituted as single or multiagent chemotherapy. Single weekly doses of methotrexate, oral chlorambucil, and intravenous etoposide have each been reported to produce complete responses in up to 33% of patients.<sup>117,118</sup> Multiagent CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisolone) or EPOCH (a combination of etoposide, prednisone, vincristine, doxorubicin, and cyclophosphamide) may produce response rates of approximately 80% of patients and complete remission reported in 38% of patients. Multiagent chemotherapy is usually reserved for patients with resistant, extensive, or advanced CTCL.

Liposomal formulations of cytotoxic agents have been shown to have more favorable pharmacokinetics, with a longer half-life circulation and greater uptake in tumor vs normal tissue. Liposomal doxorubicin at doses of 20 to 40 mg/m<sup>2</sup> every 2 to 4 weeks produces a response rate of 88.2% in patients with relapsed or refractory MF or Sézary syndrome.<sup>119</sup>

More recent therapies include histone deacetylase inhibitors (HDACs) and other chromatin remodeling

agents.<sup>120</sup> These agents modulate tumor suppressor and/or cell cycle regulatory gene expression by increasing the acetylation of histones. Suberoylanilide hydroxamic acid (SAHA) has been shown to be effective in MF. SAHA was recently approved by the FDA for refractory CTCL.

Monoclonal antibodies to CD52 (alemtuzumab) and CD4 have been used in patients suffering from advanced or refractory MF/Sézary syndrome.<sup>121,122</sup> There is an ongoing debate about toxicity, particularly cardiac toxicity associated with alemtuzumab. Currently the use of monoclonal antibodies in MF would be considered investigational.

## Conclusions

The diagnosis and treatment of CTCL remain challenging. A multitude of clinical and histopathologic presentations of the disease exist, as well as a variety of therapeutic options with a lack of randomized trials to establish efficacy. Management is further complicated by the involvement of several specialists with differing protocols, such as hematology/oncology, dermatology, pathology, and radiation oncology. An interdisciplinary center based on a stage-adapted therapeutic approach is ideal for these patients. In general, patients with early-stage disease have an excellent prognosis and should be treated with mostly skin-directed therapies. Advanced disease is associated with a poorer prognosis and usually requires systemic therapy. Patients should be encouraged when possible to enroll in controlled clinical trials until more effective and definitive treatments are found.

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