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The Management of Aggressive T-cell Lymphoma: A Discussion on Transformed Mycosis Fungoides

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Abstract

T-cell lymphomas are a diverse group of rare non-Hodgkin lymphomas. The variety of T-cell lymphomas can be grouped into 2 broad clinical categories: the usually aggressive systemic T-cell lymphomas can be included under the term *peripheral T-cell lymphoma* (PTCL), and the usually indolent T-cell lymphomas presenting in the skin can be included under the term *cutaneous T-cell lymphoma* (CTCL). Characteristics of each category can overlap. Systemic T-cell lymphomas or PTCL often present with cutaneous lesions, and CTCL can also present with systemic disease. The most precise way to communicate about these disorders is to use the specific name of the subtype. The most frequently diagnosed form of CTCL, mycosis fungoides (MF), is a primarily indolent malignancy that is most frequently managed using a variety of milder treatment approaches, such as skin-directed therapies or biologic systemic therapies. Among the MF patients who often require a more aggressive approach is a subset who develop transformed MF. Transformed MF is a rare, histologically distinct entity that can be associated with a worse prognosis. Studies are lacking to guide the optimal treatment for these patients; treatment options are generally extrapolated from the algorithms for other aggressive T-cell lymphomas or from the rare patients included in trials of therapies for CTCL. Novel agents already in development or used for MF may offer patients with transformed disease new treatment alternatives.

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Target Audience

This activity has been designed to meet the educational needs of hematologists and oncologists involved in the management of patients with mycosis fungoides.

Statement of Need/Program Overview

Mycosis fungoides (MF) is the most frequently diagnosed form of cutaneous T-cell lymphoma. It is a primarily indolent malignancy that is usually managed with milder treatment approaches, such as skin-directed therapies or biologic systemic therapies. Transformed MF is a rare, histologically distinct entity that can be associated with a worse prognosis. The transformation of MF presents clinicians with challenges in assessment, diagnosis, and treatment. Some of the novel agents used in T-cell lymphoma are effective in patients with transformed MF, but no standard treatment exists.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the differential diagnosis, optimal diagnostic techniques, and staging guidelines for mycosis fungoides
- Outline the risk factors for disease transformation
- Recognize which patients should undergo evaluation for transformation
- Outline the efficacy and safety of novel agents for the treatment of mycosis fungoides
- Define appropriate therapies for patients with transformed disease

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Introduction

Steven M. Horwitz, MD

As our understanding of the pathogenesis and biology of T-cell lymphomas has increased, so has the management of this complicated form of non-Hodgkin lymphoma. Historically, T-cell lymphomas have been treated with drugs that were "borrowed" from the treatment algorithms of other aggressive lymphomas, and these agents have been applied to the treatment of T-cell lymphomas without the benefit of large prospective trials.[1] More recent efforts have focused on the discovery and development of drugs targeted specifically to T-cell lymphomas. Some of the most successful of these efforts have come in the treatment of cutaneous T-cell lymphomas (CTCLs).

T-cell lymphomas are largely subdivided between CTCLs, which are generally more indolent, and peripheral T-cell lymphomas, which are generally more aggressive. Among the T-cell lymphomas, transformed mycosis fungoides (MF) is an example of an entity that begins as an indolent CTCL but gains characteristics that are often more aggressive in nature. In patients with underlying MF, transformed MF occurs when one population of cells undergoes a set of poorly understood molecular and/or genetic changes that confer an increased rate of growth. These cells become larger in appearance, frequently with a higher expression of CD30, and have a greater propensity for causing tumor formation and spreading to extracutaneous sites, especially lymph nodes.

The recognition of transformed MF is increasing, resulting in more patients being diagnosed with this form of T-cell lymphoma. However, the clinical meaning of the definition of transformed MF remains debatable. The histopathologic definition of transformed MF is the presence of large cells in at least 25% of the infiltrate throughout or formation of nodules.[2] Transformed MF is generally associated with a worse prognosis. Clinically, however, a spectrum is seen: some transformed MF patients have very aggressive disease, whereas others meet the definition of transformation but maintain an indolent clinical course that can be managed with milder therapies. It is difficult to give guidance as to when more aggressive approaches are necessary beyond "you know it when you see it." In general, single or minimal tumors or nontumor lesions in the skin that histologically appear to be transformed may often be managed with local radiation or other milder therapies, whereas multiple tumors or extensive lymphadenopathy or visceral disease generally require a more aggressive approach. At a minimum, an understanding of the concept of transformation in MF and an awareness of the heterogeneity of this disease's behavior go a long way toward a rational management approach to this uncommon occurrence. In the latest update of the National Comprehensive Cancer Network (NCCN) guidelines, transformed MF is specifically addressed in greater detail. A table has been added to highlight some of the systemic therapies for which there are data in transformed MF, including single-agent chemotherapies as well as some of the newer agents, such as romidepsin and pralatrexate. In addition, the NCCN algorithms now lead the reader to other therapies for aggressive T-cell lymphoma for patients with more extensive evidence of transformation.

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Clinical Perspective of Mycosis Fungoides

Madeleine Duvic, MD

A heterogeneous group of peripheral T-cell lymphomas, CTCLs initially manifest in the skin.[1] Based upon the World Health Organization (WHO) classification, a number of CTCL subtypes are now formally recognized and defined, and others are considered only provisional entities at this time.[2] The most frequently encountered form of CTCL is MF, accounting for 60% of new CTCL cases.[3] Variants and subtypes of MF include folliculotropic or syringotropic MF, pagetoid reticulosis, and granulomatous slack skin. Sézary syndrome is a less common erythrodermic and leukemic form of CTCL, comprising only 5% of MF cases. To meet current criteria for diagnosis of Sézary syndrome, a patient must have greater than 80% erythroderma as well as an elevated Sézary cell count of at least 1,000/mm^3, a CD4/CD8 ratio of 10 or greater, or a circulating population of either greater than 40% CD4-positive CD7-negative or 30% CD4-positive CD26-negative lymphs with a positive clonal TCR gene rearrangement.[3] Other CTCL subtypes include the primary cutaneous CD30-positive T-cell lymphoproliferative disorders (lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma); primary cutaneous gamma-delta T-cell lymphoma; subcutaneous panniculitic CD4-positive T-cell lymphoma; primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (provisional entity), and primary cutaneous CD4-positive small/medium T-cell lymphoma (provisional entity).[2] Although the staging system classifies most patients, there are patients who are not easily classified. Some patients meet the blood criteria for Sézary syndrome but are not erythrodermic. Also, there are patients with transformed MF who have high expression of CD30 and patients without transformed MF who also have coexisting lesions of CD30-positive lymphoproliferative disorders.

Epidemiology and Pathogenesis

A population-based study using data from the Surveillance, Epidemiology, and End Results (SEER) registry reported an overall age-adjusted annual incidence for CTCL of 6.4 million persons between 1973 and 2002.[4] This incidence represented 3.9% of all non-Hodgkin lymphomas reported in the registry, and 0.14% of cancers overall (excluding keratinocyte carcinomas). Further, the annual incidence was found to steadily increase by 2.9×10^{-6} per decade. More recently, another study using SEER registry data from 2001–2005 reported a CTCL age-adjusted incidence rate of 7.7 per 1,000,000 person-years, which was increased from 5.0 per 1,000,000 person-years during 1980–1982.[5] Both of these epidemiologic studies found marked differences in CTCL distribution, with the highest incidences in African Americans and men.

A recent study demonstrated that MF arises from skin resident effector memory T cells.[6] As with most other forms of T-cell lymphoma, the pathogenesis of MF is largely unknown. One pathway suggested for the development of MF is that the disease results from a delayed hypersensitivity reaction to a chronic, persistent environmental (viral, chemical, or infectious) or endogenous (antigenic) factor.[7] As part of the immune response, the T cells may be driven to clonally proliferate, but because they lack the pro-apoptotic Fas ligand, they exhibit loss of activation-induced cell death resulting in accumulation in the skin.[8]

Clinical Presentation, Staging, and Diagnosis of MF

The clinical presentation of MF is highly variable, and patients may present at any stage of the disease. The classic presentation begins with heterogeneous skin lesions ranging from diffuse or discreet patches or plaques to areas of dry and scaling skin.[9] White patients present with pink to red or brown lesions, whereas hypopigmentation and hyperpigmentation are seen in patients of color. Notably, these lesions tend to initially occur in sun-shielded areas (such as the groin, buttocks, medial thighs, breast, and axilla), and it is not a coincidence that phototherapy is an effective treatment for MF. Early lesions may be circular, oval, or annular, and they may or may not have scale. Lesions may coalesce over time and are frequently misdiagnosed as chronic dermatitis or eczema. Patients who present with scaly plaques (elevated lesions) are often misdiagnosed as having psoriasis. Since MF lesions are generally insidious at first, they often go unrecognized for long periods of time. Some patients with MF may progress and form tumors or develop erythroderma, which defines the later stages. Some patients present de novo with tumors, blood, or nodal involvement—skipping earlier patch-stage disease; these patients are more likely to

have histologic evidence of large cell transformation with a more aggressive course.

Variants of MF have unique clinical presentations. For example, a rare form of patch-stage MF called *poikiloderma atrophicans vasculare* is associated with epidermal atrophy with telangiectasias manifested as red, brown, and white pigmentation changes. Patients with Sézary syndrome often have keratoderma or thickening of the palms and soles, associated with tinea pedis. Severe pruritus and worsening erythroderma is often associated with *Staphylococcus aureus* colonization. Sézary patients may also develop ectropion or eversion of the eyelids, lymphadenopathy, and pedal edema.

The tumor, node, metastasis, blood (TNMB) system is the standard used for the staging and classification of MF. This system, first developed in 1975 by the Mycosis Fungoides Cooperative Group (MFCG),[10] was recently updated by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC).[11] One of the major updates revolves around the inclusion of peripheral blood involvement in addition to the traditional characteristics of skin involvement, lymph node involvement, and visceral disease. A single-center, retrospective cohort analysis of 525 patients with MF and Sézary syndrome demonstrated that the majority of patients presented with either T1 (30%) or T2 (37%) disease; the remaining presented with T3 (18%) or T4 (15%) disease.[12]

The diagnosis of MF can be difficult because early lesions have normal inflammatory T cells in addition to clonal T cells, and they overlap with other inflammatory skin disorders. According to guidelines from the NCCN, a complete skin examination, biopsy of suspicious skin sites, and immunohistochemical studies of the skin biopsy are essential components of the diagnosis of MF.[3] Histologic features that favor the diagnosis of MF include an atypical lymphocytic interface infiltrate in the papillary dermis with extension into the epidermis (epidermotropism), including lining up of haloed lymphocytes along the basal layer or collections of lymphocytes in Pautrier's microabscesses.[13] Absence of spongiosis (edema between keratinocytes) is believed to be important by many dermatopathologists, but spongiosis is not uncommon in early MF lesions. Immunohistochemistry can be very helpful in making a diagnosis of early MF. In the majority of MF cases, T cells found in the epidermis are CD4-positive and CD45RO-positive. They also express other T-cell markers, especially CD3, CD2, or CD5. The chemokine receptor CCR4 may be expressed, especially in later stages. Rare MF patients express CD8 or are double CD4CD8-positive.[3,14] Additionally, MF cells have lost specific T-cell markers such as CD7 or CD26 (limited to Sézary cells).

The workup of CTCL depends on the stage of the disease. In patients with early-stage MF (T1 and limited T2 with no adenopathy, blood involvement, or unfavorable features), the only imaging study required is a chest x-ray unless the patient has symptoms. Because there is an increase of secondary malignancies in MF patients, age-specific screening is recommended.[15] It is reasonable to perform flow cytometry at baseline staging in all patients to assess whether there is evidence of blood involvement. In advanced-stage patients, either a computed tomography (CT) scan or positron emission tomography (PET)/CT scan is recommended to assess systemic disease. A small, single-center, prospective study suggested that a PET/CT scan is more sensitive, demonstrating that it identified several patients with involved lymph nodes who would have been classified as N0 otherwise.[16] A lymph node biopsy of palpable peripheral nodes of 1.5 cm is required for complete staging, but often, core biopsy with flow can be substituted for an excision, since the latter carries risk of infection. Patients with enlarged, reactive nodes are staged at IIA, whereas patients with involved nodes are staged at IVA.

To aid in the diagnosis of early MF, the ISCL has proposed a new point-based diagnostic algorithm that incorporates clinical appearance, histopathologic characteristics, molecular biology (clonal T-cell receptor [TCR] gene rearrangement), and immunopathology.[17] The diagnosis of MF requires clinical and histologic features. This algorithm requires validation, but in the future it may allow a more standardized approach to the diagnosis of early MF.

Current Treatment Options

It is difficult to cure MF, however, the disease can be managed like a chronic skin disease in many patients. The current NCCN guidelines outline a stage-focused treatment approach.[3] Initial treatment in earlier stages (IA–IIA) is localized or generalized skin-directed therapies, whereas progressive disease requires the addition of systemic therapies (Table 1).

Stage IA MF patients generally have an excellent response to skin-directed therapy. Topical steroids should be used at the lowest effective potency. These agents can be used alone, combined, or administered with localized radiotherapy. Topical corticosteroids can achieve a high rate of complete remission,[18,19] but their long-term or generalized use may cause adverse effects: skin atrophy with telangiectasia and purpura, striae formation, and systemic absorption. The latter is seen only when high potency corticosteroids are used on large sections of skin. Topical chemotherapy (either nitrogen mustard or carmustine) has been a mainstay of early-stage MF treatment

Table 1. Treatment Regimens for Mycosis Fungoides and Sézary Syndrome

Type of Treatment		Examples
Skin-directed therapies	For limited/localized skin involvement	Topical corticosteroids Topical retinoids (bexarotene) Phototherapy (NB-UVB, PUVA) Topical chemotherapy (nitrogen mustard, carmustine) Local radiation (tumors) Experimental (lasers, PDT, imiquimod, hypericin)
	For generalized skin involvement (often combinations or with systemic biological response modifiers)	Topical corticosteroids Topical chemotherapy (mechlorethamine, carmustine) Phototherapy (NB-UVB, PUVA) Total skin electron beam therapy
Systemic therapies	SYST-CAT A	Oral retinoids (bexarotene, acitretin, isotretinoin) Interferon: alpha or gamma HDAC inhibitors (vorinostat, romidepsin, experimental) Denileukin diftitox Methotrexate Extracorporeal photopheresis Experimental: antibodies, forodesine, pralatrexate
	SYST-CAT B	Liposomal doxorubicin Gemcitabine Etoposide Pentostatin (SS only) Combination chemotherapy
Combination regimens	Skin-directed plus systemic	Phototherapy plus retinoid Phototherapy plus interferon Phototherapy plus photopheresis Total skin electron beam plus photopheresis
	Systemic plus systemic	Retinoid plus interferon Bexarotene plus denileukin diftitox Photopheresis plus retinoid Photopheresis plus interferon Photopheresis plus retinoid plus interferon

HDAC=histone deacetylase inhibitor; NB-UVB=narrow band ultraviolet B; NCCN=National Comprehensive Cancer Network; PDT=photodynamic therapy; PUVA=psoralen plus ultraviolet A; SS=Sézary syndrome.

Based on recommendations from the National Comprehensive Cancer Network.[3]

for decades; it results in high rates of response and freedom from progression.[20-22] Carmustine is less widely used because it can cause myelosuppression and generalized telangiectasia. Bexarotene, the only topical therapy that has received US Food and Drug Administration approval for MF, is a synthetic retinoid that can induce complete and partial remissions in treated index lesions.[23] Retinoids are more helpful for plaques or lesions on the hands and feet and are not well tolerated in intertriginous areas due to irritation. Retinoids such as bexarotene gel may be helpful in restoring hair growth in areas of alopecia.[24]

Phototherapy is a form of generalized skin-directed therapy used in MF patients with more extensive skin involvement.[25,26] Both UVB- and UVA-based phototherapy are effective. Psoralen plus UVA (PUVA) is most effective, but narrow-band UVB is also associated with high response rates and similar durations of relapse-free survival. Because phototherapy is associated with an increased risk of UVA-associated skin neoplasia, PUVA is generally avoided, if possible, in patients who have a history of squamous or basal cell carcinoma or melanoma.

Stage IB/IIA MF patients typically require generalized skin-directed therapy in combination with topical therapy or systemic therapy, if patients are refractory. If skin-directed phototherapy is not effective, other options include systemic biologic response modifiers or total skin electron beam therapy (TSEBT). The latter is highly effective in patients with refractory or generalized T2

(patch/plaque) or T3 (tumor) disease, but it cannot be used repeatedly.

Patients with stage IIB MF with limited extent tumor disease with or without patch/plaque disease treated with TSEBT should then receive maintenance therapy with the skin-directed therapies already described for stage I or IIA disease or systemic CAT A therapy. The NCCN guidelines recommend several systemic agents for this setting, collectively referred to as SYST-CAT A. Included within this category are retinoids (eg, bexarotene), interferons (eg, interferon-alpha or interferon-gamma), histone deacetylase (HDAC) inhibitors (eg, vorinostat and romidepsin), the combined toxin/interleukin-2 agent denileukin diftitox, methotrexate, or the immunomodulatory procedure extracorporeal photopheresis (ECP).

Patients with stage IIB MF who have generalized tumor disease, limited-extent tumor disease, or large cell transformed MF may receive TSEBT either with or without any of the other skin-directed therapies previously described or systemic therapy categorized by the NCCN guidelines within SYST-CAT B. Agents most effective for tumors include liposomal doxorubicin, gemcitabine, or HDAC inhibitors (romidepsin or vorinostat). Refractory patients may require combination chemotherapy, and if remission is achieved, they are candidates for allogeneic transplantation.

Stage III (erythrodermic MF) or Sézary syndrome (IVA or IVB) patients are treated according to the extent of blood involvement. A recent analysis of erythrodermic CTCL patients found that a Sézary cell count of greater than 10,000 was associated with a median overall survival of 2.5 years.[27] For patients with no significant blood involvement (B0), generalized skin-directed therapies (described above) with or without the addition of SYST-CAT A systemic therapy is typically used. For patients with some blood involvement (B1), systemic therapy (SYST-CAT A) in combination with mid-potency corticosteroid treatment to reduce skin symptoms is recommended. The most effective and commonly used agents in this setting are interferon alpha and/or bexarotene. HDAC inhibitors may be useful in reducing pruritus.

Sézary syndrome, bulky lymph node disease, or visceral disease are classified as Stage IV CTCL. Sézary syndrome first-line approaches combine skin-directed palliative therapy with biologic systemic therapy (SYST-CAT A; either skin-directed plus systemic treatments or combined systemic treatments). In contrast, patients with bulky lymph node or visceral disease are treated with systemic therapy (SYST-CAT B), either with or without radiotherapy and skin-directed therapy (described above). Young patients with advanced CTCL should be considered for allogeneic non-ablative transplantation as a possible curative approach.[28]

Treatment of MF in the Community Setting

MF patients often first present to dermatologists or family care physicians who have little dermatologic expertise. Since the clinical and histologic features of early MF may confound even an experienced dermatologist, it is important to have a high index of suspicion and to perform several biopsies when the patient is off therapy. Once the diagnosis is made, dermatologists are very capable of managing patients with early-stage disease that has features of a chronic inflammatory skin condition. However, if the patient progresses by developing tumors, lymph node involvement, or blood involvement, treatment by a CTCL specialist is recommended. Because MF is a very rare malignancy that may be encountered only once or twice in the career of a community oncologist, these physicians may not have the expertise to manage the patient. In particular, infections with staphylococcus may cause flares in erythroderma that abate with antibiotics rather than chemotherapy. There is a propensity for dermatologists to under-treat and for oncologists to over-treat these patients. NCCN guidelines recognize these limitations, stating that due to the rarity of MF and the need for an individualized therapeutic approach, referral to a multidisciplinary academic specialist center is preferred.[3]

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Pathologic Perspective of Transformed Mycosis Fungoides

Eric D. Hsi, MD

Both clinically and pathologically, transformed MF is a distinct entity from MF. Transformed MF is defined by a morphologic change of greater than 25% of the dermal infiltrate from small/intermediate-sized to a large cell variant (≥4 times the size of a small lymphocyte).[1,2] This transformation has been demonstrated to occur as an evolution from the original malignant clone.[3,4] Cytologically, these cells can resemble immunoblasts, large pleomorphic cerebriform cells, or even anaplastic cells. In addition to large cells, transformed MF may also appear as microscopic nodules or small sheets of larger tumor cells within a broader infiltrate.

Transformed MF: Clinical, Pathologic, and Prognostic Factors

The reported incidence of transformed MF is wide ranging (8–55%), likely reflecting the fact that it is a poorly recognized and understood condition.[5] Three studies have followed the clinical, pathologic, and prognostic characteristics of patients with transformed MF.

The first of these studies, reported by Diamandidou and colleagues in 1998, identified 26 patients with transformed MF from 115 cases of MF or Sézary syndrome diagnosed in a single clinic between 1975 and 1995.[1] Each of these patients had pathologic slides available for review. The median age at transformation was 65 years (range: 29–80 years), and the median time from the initial diagnosis of MF or Sézary syndrome to documentation of large cell transformation was 12 months (range: 0–128 months). Most patients experienced disease transformation within 2 years of MF or Sézary syndrome diagnosis. The cumulative probability of transformation from the time of MF or Sézary syndrome diagnosis was calculated to be 21% (95% confidence interval [CI], 13–29%) at 4 years, 32% (95% CI, 20–44%) at 8 years, and 39% (95% CI, 23–55%) at 12 years. No correlation was found between eventual transformation and age, sex, or incidence of peripheral blood or lymph node involvement. However, a significant association was found between transformation and elevated levels of beta-2 microglobulin or lactate dehydrogenase (P=.009), as well as stage IIIB/IV disease at referral (P=.03).

Histopathologic analysis showed that most patients (n=15) had a diffuse lymphoid infiltrate, although some patients had a lichenoid (n=5) or a patchy lymphoid

infiltrate (n=4) in the skin. The median thickness of the infiltrate was 2.15 mm (range: 0.5–10 mm, 95% CI, 1.875–4.174), and it was thicker (*P*=.0123) and more frequent (*P*=.03) in patients with T3 stage disease compared with T2 or T4 disease.

Median follow-up of surviving patients was 55 months from the time of diagnosis. It was found that transformed MF patients had a significantly shorter median survival compared to nontransformed MF or Sézary syndrome patients (37 vs 163 months; *P*=.0029). The 4-year survival was also significantly shortened (45% vs 73%; *P*=.01). Interestingly, the survival of patients with transformed stage III/IV disease was similar to that of patients with untransformed stage III/IV disease. From the time of transformation, the median survival was 19.4 months (range: 2–138 months). While the median survival was 23.5 months in patients who had undergone transformation within the first 2 years of diagnosis, it had not been reached among patients who had undergone late transformation (≥2 years after diagnosis). In addition to early versus late transformation, stage at the time of transformation was also an important prognostic factor. When combined, patients with stage IA, IB, and IIA disease at transformation had a significantly improved 2-year survival compared with combined stage IIB, III, and IV disease (86% vs 23%; *P*=.0035). Importantly, the 2-year survival rate of patients with transformed stage IIB alone was similar to that of patients with transformed stage IV disease.

The second study, reported by Vergier and colleagues in 2000, was an analysis of 45 cases of transformed MF identified by the French Study Group on Cutaneous Lymphomas between 1992 and 1998.[6] The median age at transformation was 65 years (range: 31–90 years), and most transformations occurred at least 2 years following the initial MF diagnosis (median time: 6.5 years). In all patients, the skin was the first site of transformation; an extracutaneous progression occurred in 20 patients either at the time of or within 6 months of transformation.

The proportion of large T cells out of all lymphomatous cells was between 25–49% for 7 patients, between 50–79% for 19 patients, and at least 80% for 19 patients. In each case, the transformed large cells displayed a T-cell phenotype. Approximately one-third of cases (31%) had CD30-positive large cells. Histiocytic (CD68-positive) and B-cell lymphocytic (CD20-positive) components were present in 67% and 45% of cases, respectively; these components had not been present in the previous MF biopsies for those patients.

After a median follow-up of 26.5 months, the median survival from the time of transformation was 36 months (range: 1–60 months). The 2-year, 3-year, and 5-year survival rates from the time of transformed MF diagnosis were 61.3%, 43.4%, and 20.8%, respectively. Neither age nor sex was found to be a clinically prognostic factor for survival in a univariate analysis. Interestingly, unlike in the previous study, the clinical stage at transformation was not found to be a significantly prognostic indicator for survival. However, when considered together in a multivariate analysis, age 60 years or older and clinical stage IV disease at the time of transformation were associated with a poor prognosis.

The third study, reported by Barberio and colleagues in 2007, followed 17 patients with confirmed transformed MF, comparing their clinical, histologic, and immunophenotypic features with those initially recorded when they were diagnosed with MF.[5] Patients were identified from the registry of the Hôtel Dieu Hospital in Lyon from 2000 to 2005. The median age at the time of transformation was 74 years (range: 38–83 years). The median time to transformation was 33.6 months, but it was essentially evenly divided between less than 2 years and 2 years or more from MF diagnosis (n=8 and n=9, respectively).

Among all lymphomatous cells, the proportion of large T cells was less than 79% in 4 patients and greater than 80% in 13 patients, but no patients had less than 50%. Half of the patients (n=9) had CD30-positive large cells, and 4 of these cases had high (>75% of transformed cells) CD30 expression.

The survival time from transformation ranged from 12–67 months. This study showed that advanced disease stage (IIB, III, or IV) at the time of transformation negatively affected patient prognosis; all 4 of the patients who died on-study were at stage IIB or higher at the time transformation occurred. All 4 of these patients were CD30-negative.

Differential Diagnosis of Transformed MF

The diagnosis of transformed MF is not necessarily straightforward, and it requires clinical judgment in addition to histopathologic and immunophenotyping analysis of the tissue. In some cases, it may be difficult to differentiate the large T cells from macrophages, which may also be intermediate to large in appearance. Immunostaining, particularly for the macrophage marker CD68, can be helpful in making this distinction.[7] Other cells that may require immunophenotyping to distinguish them from large tumor cells include admixed B cells.

There are rare case reports of patients with coexisting MF and a newly emerging CD30-positive primary cutaneous lymphoproliferative disorder, such as cutaneous anaplastic large cell lymphoma[8-11] or lymphomatoid papulosis.[11-13] Clinical features would be helpful in determining the appropriate diagnosis in such an event. There are also several reports of MF coexisting with Hodgkin

lymphoma.[14,15] Recognition of these distinct entities from transformed MF may require detailed immunophenotyping, molecular genetic analysis, and close clinical correlation. For example, if a clone of the new CD30-positive lesion is found to be different than the underlying MF clone at the molecular level, this is suggestive of coexisting unrelated malignancies rather than a transformation of the MF. If only a small proportion of the large cells are CD30-positive, this characteristic can be used to distinguish transformed MF from primary cutaneous anaplastic large cell lymphoma, which requires at least 75% CD30-positive large cells.[16]

Biopsy of Transformed MF

For patients with suspected transformation in the skin who already have an established diagnosis of MF, a 4-mm punch biopsy is sufficient for confirmation of transformed MF. A 4-mm punch biopsy is preferred over smaller biopsies because of the amount of tissue needed for immunophenotyping and, sometimes, molecular genetic studies. A larger excisional biopsy is needed only if the transformation is thought to be occurring deep within the lesion. In contrast, a shave biopsy has no role in lymphoproliferative disorders and should not be performed in this setting.

With regard to the lymph node biopsy, an excisional biopsy is the preferred method if clinically feasible.[17] Use of this method ensures that there is ample tissue for immunophenotyping, karyotyping, and nucleic acid isolation as needed. However, there is an increased risk of sepsis with excisional biopsy in patients with *Staphylococcus* colonization.[18] A needle core biopsy can be performed instead, but carries with it the risk of missing the involved tissue in partially involved lymph nodes.[19,20] A fine needle aspiration biopsy is useful only if it is necessary to differentiate transformed MF from some other tumor type; it can help determine if a more invasive biopsy is needed.[21]

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Clinical Overview of Transformed Mycosis Fungoides

Steven M. Horwitz, MD

Patients with transformed MF undergo changes leading them to move from a low-grade or indolent lymphoma to a more aggressive lymphoma, as can occur in other, more familiar, types of lymphoma. Transformation is not necessarily tied to the presence of tumors or the development of lymph node involvement, which reflect an increase in stage but can occur with or without the presence of transformation. Specifically in MF, transformation refers to the occurrence of a histologic change—the development of large cells. These large cells not only have a different appearance, they usually have a faster rate of growth and often carry a higher propensity to leave the skin, and often (but not always), acquire CD30 expression.

Transformed MF: Prognosis

To correctly compare the prognosis of transformed MF patients with their nontransformed MF counterparts, one must correct for stage. A retrospective analysis of patients with MF or Sézary syndrome was conducted to compare the long-term outcomes of patients with advanced stage disease (n=92) and large cell transformation (n=22) from a single center during 1976–2007.[1] Among patients with advanced stage disease (stages III/IV), 48% had experienced disease progression (including large cell transformation), with a median time to progression of 4.5 years (range: 1 month–29 years). The median overall survival (OS) was 5 years in these patients, with 2-year, 5-year, and 10-year OS rates of 66%, 49%, and 32%, respectively. Patients with transformed MF had poorer outcome than the patients with advanced stage disease who had no evidence of transformation (median OS: 2.2 vs 5.2 years, respectively). Although there was a trend toward a better outcome among transformed MF patients with CD30-positive disease compared with CD30-negative disease, it was not significant.

It is important, however, to remember that patients with transformed MF patients are heterogeneous, and a range of outcomes may occur; some transformed MF patients have relatively indolent disease or localized transformation, and even spontaneous regression can occur. Therefore, treatments should be individualized, and aggressive therapy is often but not always warranted.

Transformed MF: Treatment Options

Once a patient has developed transformed MF, the level of treatment is generally sufficiently complex to warrant the need of a specialist for patient care. These patients often have areas of aggressive disease, as well as areas that have not transformed and may still respond to skin-directed treatments. Therapies for transformed MF often include systemic agents with demonstrated activity in transformation or those used for other aggressive T-cell lymphomas (Table 1). There is a lack of prospective data to guide the best therapy, and experts in treating CTCL can provide useful experience in combining appropriate systemic therapy for transformed disease with other skin-directed therapy. In these patients, a consultation at a specialty clinic may be helpful to establish the treatment plan.

One common scenario would be for an MF patient with skin involvement only to develop a new tumor with a biopsy showing evidence of large cell transformation. It would be appropriate at this time to restage this patient with imaging studies. PET/CT is often preferred to CT alone in terms of identifying suspicious nodal or visceral involvement and to guide biopsies. Local radiotherapy is an effective treatment for the eradication of a single or localized area of transformed disease on the skin. Postradiation therapy often may be attempted with mild systemic therapies such as bexarotene, methotrexate, HDAC inhibitors, or interferon in an attempt to maintain remission. However, other options include

Table 1. Suggested Therapies for Transformed Mycosis Fungoides From the NCCN

Category C (SYST-CAT C)
• Liposomal doxorubicin
• Gemcitabine
• Denileukin diftitox
• Romidepsin
• Low- or standard-dose pralatrexate

NCCN=National Comprehensive Cancer Network.

Adapted from the National Comprehensive Cancer Network.[10]

observation alone or continuation of the skin-directed therapy that the MF patient was receiving prior to transformation.

Patients with multiple areas of skin involvement with transformed disease or extracutaneous transformed disease require systemic therapy. Pralatrexate was evaluated in the phase II PROPEL (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma) study, which included patients with aggressive T-cell lymphomas, including transformed MF patients. At a dose of 30 mg/m^2/week for 6 weeks in a 7-week cycle, pralatrexate demonstrated activity in 12 patients with transformed MF, with an investigator assessed response rate of 58%.[2] In a subsequent dose-finding study, which also included transformed MF patients, lower doses of pralatrexate (15 mg/m^2/week for 3 weeks in a 4-week cycle) were found to be effective as well.[3]

Romidepsin is currently approved for the treatment of CTCL, and studies evaluating romidepsin in aggressive T-cell lymphomas have also included patients with transformed MF. While we do not have specific response rates for patients with transformed MF treated with romidepsin, evidence of its activity in patients with aggressive T-cell lymphomas suggests a role in patients with transformed MF as well.[4,5]

Denileukin diftitox is another option for treating transformed MF. It is currently approved for CTCL and has not been studied specifically in transformed MF. However, a recent phase II trial showed a reasonable response rate with denileukin diftitox in patients with peripheral T-cell lymphoma, suggesting this agent may have activity in more aggressive disease.[6]

Mild therapies used to treat CTCL, such as extracorporeal photopheresis, phototherapy, or the monoclonal antibody alemtuzumab, are probably less effective for the treatment of transformed MF and seem to have less activity in tumors or faster growing lesions. However, this approach has not been tested in clinical studies.

There are limited data regarding the use of combination therapies in the treatment of transformed MF. The duration of response in many patients is often short. Therefore, single-agent or milder combinations, if effective, have the advantage of being able to be continued to maintain responses without cumulative toxicity. Combination chemotherapy may be useful for patients who are not easily controlled with milder therapies, and allogeneic stem cell transplant may also be an option for those patients who achieve good disease control in this otherwise poor prognosis situation. The best candidates for this procedure are patients with good skin integrity who are in a minimal or controlled disease state at the time of transplant.[7] Radiation is often useful prior to stem cell transplant to achieve remission or a minimal disease state.

Induction therapy with pegylated liposomal doxorubicin is currently being evaluated in an ongoing clinical trial in CTCL patients, some of whom have aggressive disease.[8] In this trial, liposomal doxorubicin is used to induce a remission, followed by maintenance bexarotene. This approach is an option for patients to be treated with more aggressive therapy to induce a remission, and then switched to a better tolerated agent to maintain that remission.

Novel combinations may offer promise in the future treatment of transformed MF. The proteasome inhibitor bortezomib is being evaluated combined with the HDAC inhibitor vorinostat in a European study to determine if the combination is more effective than either agent alone. Other proposed combinations involve newer agents such as romidepsin, pralatrexate, and lenalidomide. SGN-35, an anti-CD30 antibody-drug conjugated to the tubulin inhibitor auristatin, is not yet approved but has been investigated in early studies in both Hodgkin lymphoma and anaplastic large cell lymphoma. Because many transformed MF patients have increased CD30 expression in their transformed cells, there is great interest in evaluating SGN-35 in this setting.[9]

Due to the rarity of this condition, it is unlikely that there will be large, randomized clinical studies in the near future that will compare different treatment regimens in transformed MF. Thus, the most practical approach is to apply principles learned from data in aggressive T-cell lymphomas.

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Question and Answer Forum

What is the definition of transformed MF?

Eric D. Hsi, MD Although it is a rarely encountered disease, transformed MF is clearly defined. A diagnosis of transformed MF may be made in MF patients who exhibit a morphologic change of at least 25% of the dermal infiltrate from small/intermediate-sized lymphocytes to a large cell variant (≥4 times the size of a small lymphocyte). By definition, transformed MF occurs only in patients with underlying MF, which can aid in the differential diagnosis of transformed MF. The expression of CD30 may or may not be present in transformed MF but when present may be difficult to distinguish from anaplastic large cell lymphoma, histologically.

What is the prognosis of patients with transformed MF?

Eric D. Hsi, MD Overall, transformed MF patients have a poor prognosis, especially when compared with their counterparts with nontransformed MF. Three studies have retrospectively evaluated the prognosis of transformed MF patients, reporting survival times that were significantly lower than nontransformed MF patients. When determining prognostic factors for survival, the trials were slightly discordant and thus require further study. However, potential prognostic factors that have been identified include advanced (stage III/IV) MF disease at the time of transformation, and transformation at or within 2 years from MF diagnosis.

What is the optimal treatment approach for patients with transformed MF?

Steven M. Horwitz, MD Unfortunately, there is no standard of care for the treatment of transformed MF. The care of transformed MF patients is further complicated by the fact that there have been no large, randomized or prospective studies that have compared one therapeutic approach or agent with another. Therefore, physicians must rely on their experience with treatments for other aggressive T-cell lymphomas, such as advanced stages of MF. Thus, systemic therapy is likely the wisest course of action, although stem cell transplant may also be an option in appropriate patients.

However, it is important to remember that transformed MF is a heterogeneous disease, presenting differently in various patients. Thus, the treatment of transformed MF requires an individualized approach, whereby higher potency treatments are reserved for aggressive disease, and residual indolent areas (which may not have undergone transformation) may be treated with less toxic, less potent skin-directed therapies.

How should MF and transformed MF be managed in the community setting?

Madeleine Duvic, MD Due to the rarity of the condition, guidelines from the NCCN recommend that all patients with CTCL be cared for in a multidisciplinary academic center with experts familiar with CTCL. Patients with early stages of MF often present to their dermatologists, who are generally well equipped to treat these patients with local skin-directed therapies. However, as the disease progresses, treatment becomes increasingly complex. This is especially true for transformed MF. Without the availability of standard recommended treatments or clinical data establishing the safety and efficacy of particular therapies in transformed MF, patients with this form of MF are best managed under the care of an expert with prior experience.

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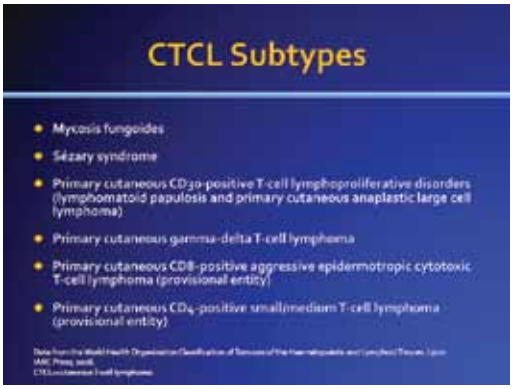

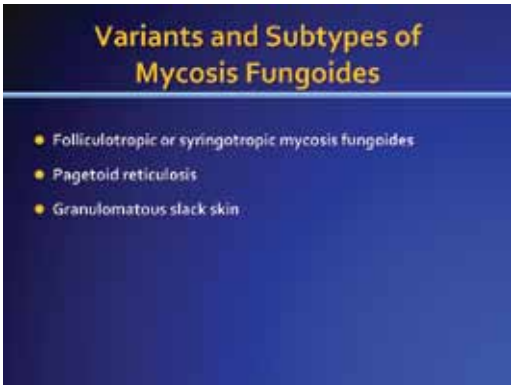

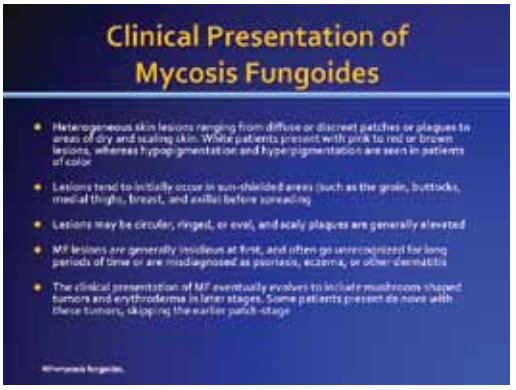

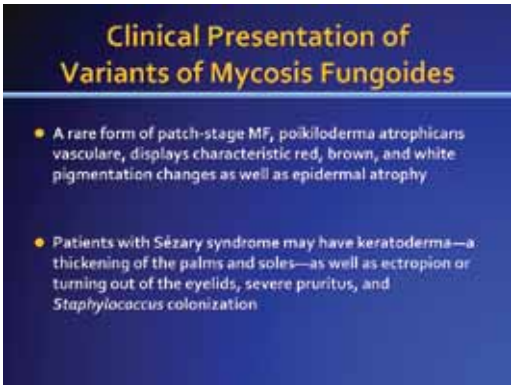

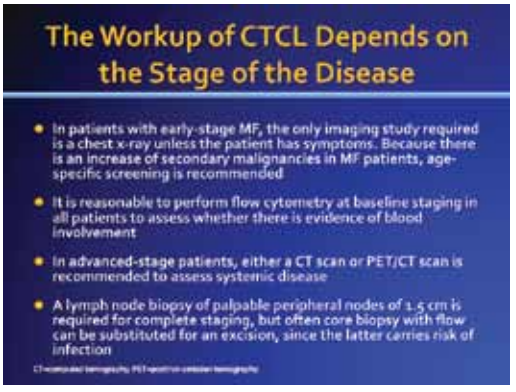

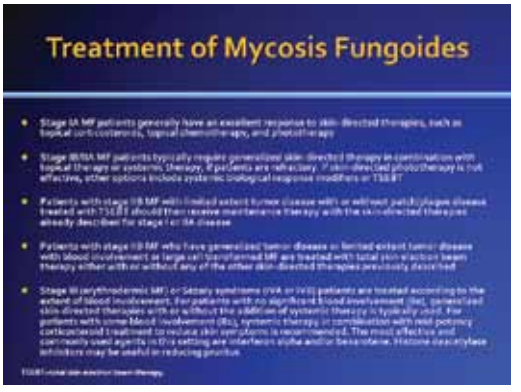

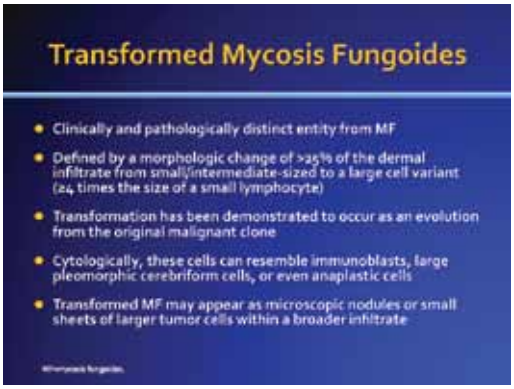

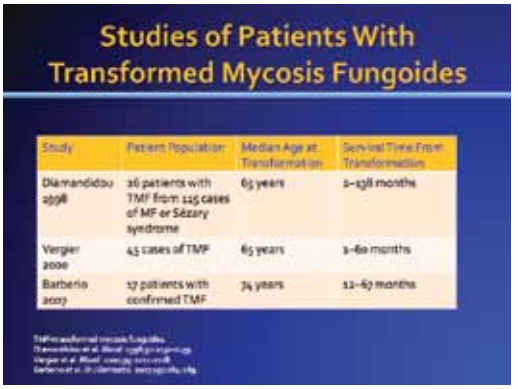

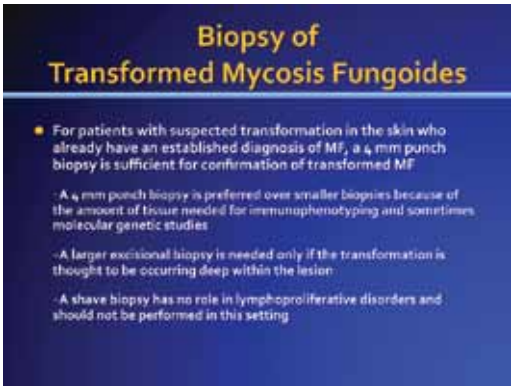

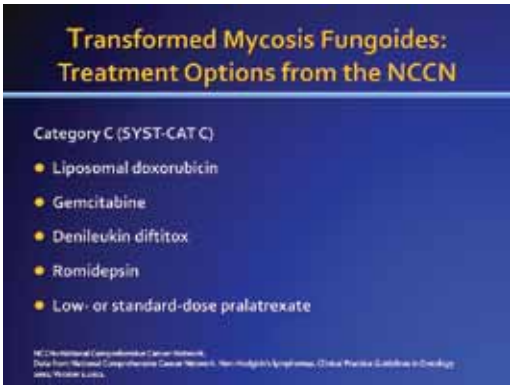

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