

A Young Man with a Persistent Skin Eruption

Christina G. Kendrick, MD; Michelle S. Gerdes, MD;
Fred A. Lopez, MD, FACP; and Elizabeth I. McBurney, MD, FACP

There are many types of skin disease that fit into the classification of cutaneous lymphoma, but mycosis fungoides is by far the most common of this group. It is a non-Hodgkin's lymphoma of T-cell origin that presents in the skin. Mycosis fungoides often evolves for years without a specific diagnosis because it can present as an eczematous or psoriasiform eruption. Patients identified in the early stages and treated appropriately have a normal life expectancy.

In 1986, a 13-year-old white boy presented to the dermatology clinic with a 1-year history of a pruritic eruption on his skin. Examination at that time revealed excoriated erythematous papules and patches in the axillae, groin, back and face. An oil preparation of lesional skin scrapings was negative for scabietic mites; however, based on clinical appearance, the patient was treated empirically for scabies with lindane lotion. The treatment did not lead to improvement in the skin findings or the pruritus. He was later diagnosed as having nummular eczema and underwent therapy with various topical steroids, again without improvement. Later he received a combination of oral psoralens plus ultraviolet-A light, but his rash continued to evolve over the next two years.

In 1988 he was hospitalized with a scaly, erythematous and lichenified patchy dermatitis of his trunk, proximal extremities, anterior neck and popliteal fossa (Figure 1). In addition, there were 2-3 mm erythematous pap-

ules on the trunk that were both within and separate from the underlying dermatitis. A firm right inguinal node measuring 1.5 x 1 cm was noted. Dermatology was consulted. Biopsy of the skin lesions revealed a psoriasiform lymphoid infiltrate with mild to moderate T-cell dysplasia consistent with cutaneous T-cell lymphoma. Special leukocyte monoclonal antibody studies performed on the skin biopsy specimens were positive for T-cell markers, again consistent with a T-cell lymphoma. The biopsy of the inguinal lymph node revealed only intense hyperplasia with a nodular paracortical pattern consistent with dermatopathic changes. There was no evidence of T-cell lymphoma within the lymph node. A chest x-ray was normal. CT scan showed no evidence of adenopathy in the abdomen or pelvis, but there were several mildly enlarged nodes in both inguinal regions. Complete blood count revealed a white blood cell count of 5700/ μ L (6000-11000/ μ L), hemoglobin 15.6 gm/dL

CME INFORMATION

TARGET AUDIENCE

The March/April Clinical Case of the Month is intended for family physicians, general internists, general practitioners, dermatologists, emergency medicine physicians, pediatricians, radiologists, and medicine subspecialists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature from the Department of Medicine at the LSU Health Care Sciences Center. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, clinical presentation, diagnosis, and treatment of mycosis fungoides.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Kendrick has nothing to disclose.
Dr. Gerdes has nothing to disclose.
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.
Dr. McBurney has nothing to disclose.

ORIGINAL RELEASE DATE

4/1/2004

EXPIRATION DATE

4/30/2005

Estimated time to complete this activity is 1 hour.

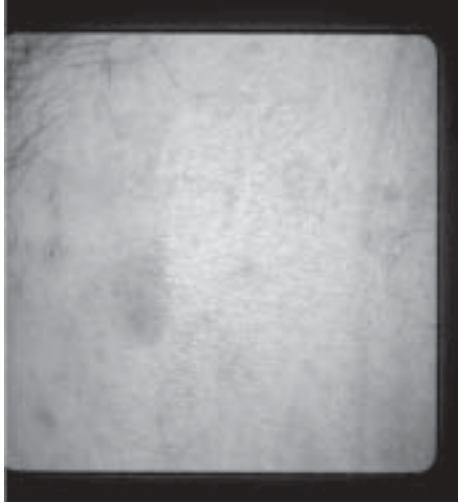


Figure 1. An erythematous plaque with overlying fine scale on the trunk.



Figure 2. A representative example of an erythematous plaque in the axilla, a common area of presentation of mycosis fungoides.

(13.5-17.5 gm/dL), hematocrit 45.3% (40%-51%), and platelet count 173,000/ μ L (130,000-400,000/ μ L). A complete metabolic profile was normal. A blood smear showed no evidence of malignant circulating T-lymphocytes. Serum immunoglobulin A, G, and M levels were normal. Bilateral iliac crest bone marrow aspirate and biopsy showed no evidence of lymphoma.

Based on the clinical and histopathological findings, he was diagnosed with cutaneous T-cell lymphoma, specifically mycosis fungoides, with no evidence of extracutaneous disease. He was initiated on therapy consisting of topical nitrogen mustard. His skin lesions and the pruritus improved until 1992, at which time he was lost to follow-up.

The patient was seen again in 2003 when he presented with new patches in the groin, axillae, and back that exhibited poikiloderma (atrophy, hyperpigmentation, hypopigmentation and telangiectasias). There was no lymphadenopathy or organomegaly. A systemic work-up was again negative for malignancy. Currently using only pimecrolimus cream 0.1%, the patient reports good control of his pruritus.

MYCOSIS FUNGOIDES – AN OVERVIEW

The term *Mycosis fungoides* (MF) was first coined by a French baron named Jean Louis Alibert in the early 1800s. He chose this name because of the “mushroom-type” skin lesions that he noted which resembled a fungus.¹ In 1938, Sézary and Bouvrain found that the skin and blood of these patients contained abnormal cells that were hyperchromatic and convoluted. These cells later came to be known as “Sézary cells,” manifesting a serpentine or cerebriform nucleus with condensed heterochromatin at the periphery.² It was not until the early 1970s, however, that this cell was found to be an abnormal lymphocyte of

T-cell origin. Since the time of this discovery, our insight into this disease has progressed rapidly.³

MF is a disease of malignant, skin-targeting T cells. It is part of a group of non-Hodgkin's lymphomas known as cutaneous T-cell lymphomas (CTCLs). Although the term MF has erroneously been used interchangeably with CTCL, it is important to recognize that there are forms of CTCL other than MF. The CTCLs are classified by clinical presentation, histologic features such as cell size and differentiation, immunophenotypic markers, and response to treatment. The group of CTCLs includes MF, Sézary syndrome (the leukemic form of MF), primary cutaneous CD30+ lymphoproliferative disorders, peripheral T-cell lymphomas, extranodal natural killer cell/T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma.⁴ Nonetheless, MF represents the vast majority of the CTCLs and will be the focus of this review.

EPIDEMIOLOGY, CLINICAL PRESENTATION AND COURSE

The incidence of MF increases with advancing age, with the peak age of onset between 55-60 years of age. It is seen about twice as often in men and blacks as in women and whites, respectively. A typical patient will present with flat erythematous patches or even raised, scaly plaques that are pruritic. At this stage, the disease presentation is nonspecific and can elude diagnosis for years. Patients are often misdiagnosed with common skin disorders such as eczema, atopic dermatitis, contact dermatitis, tinea corporis, or psoriasis that is “resistant” to therapy. The patches and plaques of MF can persist for years, or spontaneously resolve. Some of the lesions can exhibit poikiloderma consisting of the triad of epidermal atrophy, telangiectasias, and mottled hyperpigmentation. When the atrophy develops, it appears that the skin has

fine wrinkling like that seen with cigarette paper. The classic distribution of lesions of MF is on unexposed sites over the buttocks, groin, axillary and inframammary areas (Figure 2). In general, it is helpful to think of the disease as manifesting in areas covered by two layers of clothing. This distribution can be very useful in ruling out other causes of chronic dermatitis and highlights the importance of a full body skin exam in making this diagnosis.^{5,6}

The evolution of disease and skin changes is typically from patches and plaques to tumors and then erythroderma. After the initial presentation, there is an orderly progression from limited patches to more generalized patches and plaques. The plaques are sharply demarcated, but can coalesce with other lesions to form serpiginous patterns. With time, central clearing of the lesions can give an annular appearance like that of tinea corporis.

A more advanced stage of the disease is evidenced by tumors. These have a predilection for the same areas mentioned previously, but are also often found on the head and neck. These exophytic masses are reddish-

brown to purple and can ulcerate, often followed by secondary infection and septicemia.⁷

The erythroderma stage can arise de novo or can evolve in patients with previously diagnosed MF. These patients have generalized erythroderma with very lichenified or atrophic skin. Pruritus is often the complaint that brings these patients to seek medical attention. About half of patients with erythroderma have atypical cells (Sézary cells) in the blood at the time of diagnosis. If the patient manifests the triad of erythroderma, lymphadenopathy, and significant numbers of circulating Sézary cells in the blood, they are said to have Sézary syndrome (SS), the leukemic form of MF. Other associated findings in SS are alopecia, palmoplantar hyperkeratosis, dystrophic nails, eyelid edema, ectropion, and leonine facies.^{8,9}

The chance of developing extracutaneous disease is directly related to the degree of skin involvement. It is highly unusual for a patient with limited numbers of patches and plaques to have extracutaneous disease. The malignant T cells can affect any organ, although extracutaneous involvement generally becomes apparent as lymphadenopathy in areas of significant cutaneous disease. Only about 8% of those with generalized plaques have extracutaneous disease while patients with tumors or erythroderma have it more than 33% of the time.⁶

DIAGNOSIS

Histologic verification of disease in the early stages of MF can be very difficult. In fact, many initial biopsies are read as "nonspecific dermatitis." Therefore, if there is strong clinical suspicion of MF, it is important to take multiple punch biopsies at 3-month intervals until a more definitive diagnosis can be made. In the early stages, a sparse lymphocytic infiltrate in the epidermis and papillary dermis is seen. By the plaque stage, a more band-like subepidermal infiltrate of Sézary cells is seen. By the tumor stage, the malignant cells are found packed deeper in the dermis, and rarely, a granulomatous response can be seen.^{10,11}

TABLE 1. TNM Classification of Cutaneous T-Cell Lymphoma (CTCL)	
Classification	Description
T: Skin	
T0	clinically and/or histopathologically suspicious lesions; not diagnostic of CTCL
T1	limited plaques, papules, or eczematous patches covering <10% of skin surface
T2	generalized plaques, papules, or eczematous patches covering ≥10% of skin surface
T3	Tumor(s)
T4	generalized erythroderma
N: Lymph Nodes	
N0	no clinically abnormal peripheral lymph nodes; pathology negative for CTCL
N1	clinically abnormal peripheral lymph nodes; pathology negative for CTCL
N2	no clinically abnormal peripheral lymph nodes; pathology positive for CTCL
N3	clinically abnormal lymph nodes; pathology positive for CTCL
M: Visceral Organs	
M0	no visceral organ involvement
M1	visceral involvement
PB: Peripheral Blood	
B0	atypical circulating cells not present (<5%)
B1	atypical circulating cells present (>5%)

*Adapted from Bunn and Lamberg (1979)¹⁷

Table 2. Staging of CTCL			
Stage	T	N	M
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 and Lamberg (1979)¹⁷

Due to the difficulty in making a histologic diagnosis of MF in the early stage of disease, many ancillary tests have been developed to corroborate clinical and histologic suspicion. Immunophenotyping involves application of monoclonal antibodies to frozen tissue sections of lesional skin. Antibodies are applied against markers for T cells and T-cell subsets (such as CD4 and CD8). The neoplastic T-cells in MF typically express the immunophenotypic pattern of CD3 and CD4 positivity while being CD8 and CD7 negative; exceptions can occur. Other tests that can be performed are T-cell receptor gene rearrangements, flow cytometry of peripheral blood, and electron microscopy.¹²⁻¹⁶

In order to check for blood involvement, peripheral blood smears can be evaluated for abnormal lymphocytes. If greater than 5-20% of circulating lymphocytes are Sézary cells, blood involvement is likely. One diagnostic problem with using this test alone is that it is unable to distinguish between polyclonal and clonal T-cell populations.¹⁷⁻¹⁹

CLASSIFICATION, STAGING, AND PROGNOSIS

In 1978 the National Cancer Institute established the staging criteria that are still used today (Tables 1 and 2).²⁰ As part of an initial staging evaluation, careful examination of the skin, particularly the non-exposed areas, should be performed. The exam should also include a complete lymph node exam and evaluation for hepatosplenomegaly. Skin biopsy, CBC, peripheral blood flow cytometry for T-cell subsets, serum chemistries, and chest x-ray should also be ordered. If lymphadenopathy is noted, a lymph node biopsy is indicated. Other than x-ray, further imaging studies of patients with stage I to IIA disease in the absence of peripheral lymphadenopathy are unwarranted. Bone marrow involvement is usually demonstrated by visualization of Sézary cells in the peripheral blood; bone marrow biopsy may not be necessary. Additional staging procedures for patients with advanced disease include computed tomographic scans of the chest, abdomen, and pelvis.²¹

Due to the rarity of this disease, studies evaluating prognostic factors are often limited by small sample size and confounding factors. Factors that have been correlated with poorer survival are age > 60 years, advanced skin disease, lymphadenopathy, bone marrow infiltration, high lactate dehydrogenase levels, high β_2 -microglobulin levels, and transformation to large cell lymphoma.²² Almost no stage IA patients die from MF, and only 9% of these patients will advance to a higher stage of disease. IB and IIA patients have a 24% likelihood of disease progression and nearly 20% die of causes related to MF. Stage IIB and III patients have a median survival of 3-5 years. The majority of these patients will die of MF. Stage IV patients have a median survival of < 30 months.^{6,22}

In general, patients die of causes other than their MF.

In fatal cases, many patients die as a result of an infected skin lesion that leads to bacteremia with *Staphylococcus aureus* or *Pseudomonas aeruginosa*.⁵

TREATMENT

In deciding upon appropriate treatment, several factors are considered: stage of disease, prognostic factors, accessibility, and cost-to-benefit ratio. Control of the pruritus is paramount. Emollients and oral antipruritics should be used as needed. In the early stages of disease, one of the adjunctive treatments utilized is a topical steroid. Interestingly, the patients that are initially misdiagnosed as having eczema or psoriasis are often treated initially with topical steroids. In general, however, if a patient does not show marked improvement or continues to progress despite this therapy, the diagnosis of MF should be considered. Once a definitive diagnosis of MF has been made, referral to a dermatologist should be made so that MF-targeted therapies can be initiated. Treatment decisions are complex and depend greatly on the clinical stage of disease. Topical nitrogen mustard, topical carmustine, topical bexarotene, electron beam therapy, phototherapy, interferon- α , systemic retinoids, systemic combination chemotherapy, and even hematopoietic cell transplantation individually or in combination have been used to treat patients with MF.^{6,23} Importantly, MF-directed therapy in patients with biopsy findings merely suggestive of MF is not appropriate.⁷

REFERENCES

1. Alibert JLM. *Description des maladies de la peau; observées à l'Hospital St. Louis*. Paris, Barrois L'aine et Fils; 1806:157.
2. Sézary A, Bouvrain Y. Erythrodermie avec présence de cellules monstrueuses dans le derme et dans le lang circulant. *Bull Soc Fr Dermatol Syph* 1938;45:254-260.
3. Crossen PE, Mellor JL, Finley AG, et al. Sézary Syndrome: cytogenetic studies and identification of the Sézary cell as an abnormal lymphocyte. *Am J Med* 1971;50:24-34.
4. Willemze R. Cutaneous T-cell lymphoma. In: JL Bologna, JL Jorizzo, RP Rapini (editors). *Dermatology*. Spain: Elsevier Science; 2003: 1922.
5. Kuzel TM, Roenigk HH, Rosen ST. Mycosis fungoides and the Sézary syndrome: A review of pathogenesis, diagnosis, and therapy. *J Clin Oncol* 1991;9:1298-1313.
6. Kim YH, Hoppe R.T. Mycosis fungoides and the Sézary syndrome. *Seminars in Oncology* 1999;26:276-289.
7. Duvic M, Cather JC. Emerging new therapies for cutaneous T-cell lymphoma. *Dermatol Clin* 2000;18:147-156.
8. Jones GW, Rosenthal D, Wilson LD. Total skin electron radiation for patients with erythrodermic cutaneous T-cell lymphoma (mycosis fungoides and the Sézary syndrome). *Cancer* 1999;85:1985-1995.
9. Zackheim HS, Epstein EH Jr. Low-dose methotrexate for the Sézary syndrome. *J Am Acad Dermatol*, 1989;21:757-762.
10. Sanchez JL, Ackerman AB. The patch stage of mycosis fungoides: criteria for histologic diagnosis. *Am J Dermatopathol* 1979;1:5-26.

11. Buechner SA, Winkelmann RK. Sézary syndrome: a clinicopathologic study of 39 cases. *Arch Dermatol* 1983;119:979-986.
12. Izbán KF, Hsi ED, Alkan S. Immunohistochemical analysis of mycosis fungoides on paraffin-embedded tissue sections. *Mod Pathol* 1998;11:978-982.
13. Willemze R, Kerl H, Sterry W, et al. Diagnostic criteria in Sézary syndrome: a multiparameter study of peripheral blood lymphocytes in 32 patients with erythroderma. *J Invest Dermatol* 1983;81:392-397.
14. Fucich LF, Freeman SF, Boh EE, et al. Atypical cutaneous lymphocytic infiltrate and a role for quantitative immunohistochemistry and gene rearrangement studies. *Int J Dermatol* 1999;38:749-756.
15. Veelken H, Wood GS, Sklar J. Molecular staging of cutaneous T-cell lymphoma: evidence for systemic involvement in early disease. *J Invest Dermatol* 1995;104:889-894.
16. McNutt MS, Crain WR. Quantitative electron microscope comparison of lymphocyte nuclear contours in mycosis fungoides and in benign infiltrates in the skin. *Cancer* 1981;47:698-709.
17. Bunn PA Jr, Lamberg SI. Report of the committee on staging and classification of cutaneous T-cell lymphomas. *Cancer Treatment Reports* 1979;63:725-728.
18. Boulouc A, Wechsler J, Delfau-Larue MH, et al. Sézary syndrome revealed by routine blood examination. *Br J Dermatol* 1999;141:747-776.
19. Russell-Jones R, Whittaker S. T-cell receptor gene analysis in the diagnosis of Sézary syndrome. *J Am Acad Dermatol* 1999;41:254-259.
20. Bunn PA Jr, Lamberg SI. Report of the committee on staging and classification of cutaneous T-cell lymphomas. *Cancer Treatment Reports* 1979;63:725-728.
21. Sibaud V, Beylot-Barry M, Thiebaut R, et al. Bone marrow histopathologic and molecular staging in epidermotropic T-cell lymphomas. *Am J Clin Path* 2003;119:414-423.
22. Diamandidou E, Colome M, Fayad L, et al. Prognostic factor analysis in mycosis fungoides/Sézary syndrome. *J Am Acad Dermatol* 1998;40:914-924.
23. Breneman D. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. *Arch Dermatol* 2002;138:325-332.

Dr. Kendrick is Chief Resident in Dermatology at Louisiana State University School of Medicine in New Orleans. **Dr. Gerdes** is a house officer in the Department of Dermatology at Louisiana State University School of Medicine in New Orleans. **Dr. Lopez** is Associate Professor of Medicine, Section of Infectious Diseases, Department of Medicine, Louisiana State University School of Medicine in New Orleans. **Dr. McBurney** is Clinical Professor of Dermatology at LSU School of Medicine and Tulane University School of Medicine in New Orleans.

The **Clinical Case of the Month** is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical Students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions.

CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 111. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to April 30, 2005. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the following are true of Sézary cells *except*:
 - a) In patch and plaque stage mycosis fungoides, they are found migrating into the epidermis.
 - b) They are of T- or B-cell origin.
 - c) They have a cerebriform nucleus with condensed heterochromatin at the periphery.
 - d) A patient who has significant numbers of these in the blood, along with erythroderma and lymphadenopathy, is classified as having Sézary syndrome.
2. Regarding the prognosis of patients with mycosis fungoides, all of the following are true *except*:
 - a) Most patients with mycosis fungoides will not die from this disease.
 - b) In fatal cases of mycosis fungoides, the majority die of septicemia secondary to infected skin lesion.
 - c) Patients with lymphadenopathy have a worse prognosis.
 - d) Patients who are younger than 60 years of age have a worse prognosis.
 - e) Patients who present with tumors as the first manifestation of disease have a worse prognosis.
3. MF patients can present with skin lesions similar to all of the following *except*:
 - a) Psoriasis
 - b) Contact dermatitis
 - c) Eczema
 - d) Squamous cell carcinoma
 - e) Tinea corporis
4. MF and Sézary syndrome patients often first seek medical attention because of:
 - a) headaches
 - b) pruritus
 - c) shortness of breath
 - d) seizures
 - e) abdominal pain