

Diverse cutaneous manifestations associated with a single disease

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Three patients had diverse clinical manifestations, all relating to the same disease (Figures 1–3). A representative skin biopsy is seen in Figure 4. What is the diagnosis, and what therapeutic options should be considered?



Figure 1. Scaly, red pruritic patches on the buttocks.



Figure 2. Violaceous tumors on the left anterior abdomen.



Figure 3. Generalized exfoliative erythroderma.

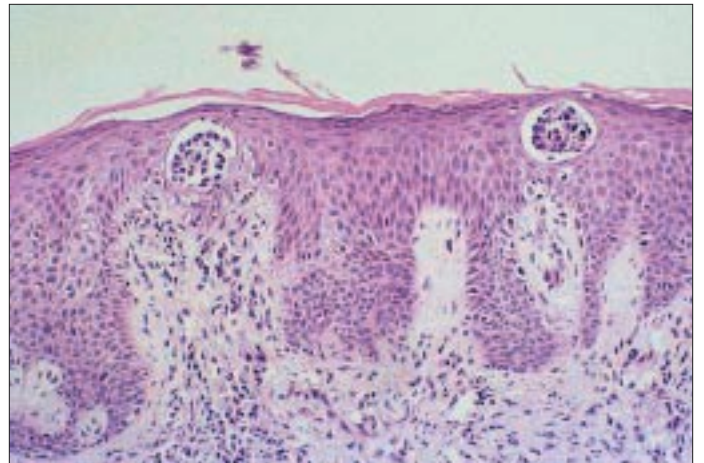


Figure 4. Routine histopathology slide from the patient shown in Figure 1 (hematoxylin-eosin stain, x40).

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DIAGNOSIS: Mycosis fungoides.

DISCUSSION

Approximately two thirds of cutaneous lymphomas are of T-cell origin. Cutaneous T-cell lymphoma (CTCL) comprises a heterogeneous group of malignancies, the most common form of which is mycosis fungoides (MF) (*Table 1*). MF is a rare, low-grade lymphoma with an estimated incidence of 0.36 cases per 100,000 people (1). Approximately 1000 new cases are found yearly. The incidence in African Americans is 1.6 that in Caucasians. Men are affected twice as often as women (1).

Clinically, early lesions of MF present as scaly, red patches or plaques in double-covered areas such as the buttocks (*Figure 1*), groin, or breasts. In ethnic patients, hyper- and hypopigmentation from the lesions may be striking and of great concern to affected individuals. More advanced cutaneous lesions consist of tumors (*Figure 2*) and a generalized exfoliative erythroderma (*Figure 3*). When erythrodermic patients have >10%–20% circulating atypical lymphocytes, they may be classified as having Sézary syndrome.

Patients typically have nondescript “rashes” for years prior to diagnosis and are misdiagnosed as having common inflammatory dermatoses like eczema, lupus erythematosus, tinea, pityriasis rubra pilaris, or psoriasis. In the early stages, pathology of involved areas likewise may be indeterminate (see Diagnostic procedures).

Pathogenesis

The cause of MF is unknown; however, many consider chronic antigenic stimulation (2) and defective apoptosis (3) important in the pathogenesis. MF is a malignancy of skin-homing memory T lymphocytes (4). Usually the malignant lymphocytes are CD4⁺CLA⁺; however, CD8⁺ variants do exist (5). MF usually arises from one malignant clone; hence, diagnosis can be aided by obtaining molecular biology studies of the T-cell receptor. Initially, the cells are epidermotropic (migrate to skin); however, with time the malignant T cells lose their affinity for skin and may disseminate internally (6).

Diagnostic procedures

To rule out the possibility of MF, a biopsy should be taken of any chronic rash that has been refractory to traditional topical therapy. For the most accurate results, biopsies should be performed when patients have been off therapy for at least 2 weeks. More information will be found if biopsies are done on the thickest lesions found in sun-protected areas like the buttocks. The histopathologic diagnosis of MF is difficult and requires an experienced dermatopathologist (7, 8). When MF is strongly suspected, repeat biopsies may be required at 6-month intervals for definitive diagnosis. On histopathology, small sheets of lymphocytes abutting the dermal-epidermal junction and collections of atypical lymphocytes in the epidermis (Pautrier’s microabscesses, *Figure 4*) are helpful in the diagnosis of MF.

Adjunctive tests may be required if the diagnosis cannot be determined from routine slides stained with hematoxylin-eosin. For patients with lesions highly suspicious for MF but with equivocal or nondiagnostic histopathology, immunophenotyping will frequently provide more information (9). The most common

Table 1. T-cell lymphomas involving the skin

| |
|--|
| Cutaneous T-cell lymphomas |
| • Mycosis fungoides |
| • Sézary syndrome (leukemic variant of mycosis fungoides) |
| • CD30 (Ki-1) ⁺ large-cell lymphomas (includes pleomorphic, anaplastic, and immunoblastic variants) |
| • CD30 ⁻ large-cell lymphomas (includes pleomorphic, anaplastic, and immunoblastic variants) |
| Human T-lymphotropic virus type 1-related T-cell disorders |
| Peripheral T-cell lymphoma (includes subcutaneous panniculitis-like lymphoma) |
| Natural killer cell lymphoma (CD56 ⁺) |

phenotype is CD2⁺CD3⁺CD4⁺CD5⁺CD7⁻CLA⁺CD45RO⁺. Additionally, immunophenotyping may detect CD8⁺ variants, which express CD7 but lack CD2 and may have a more aggressive clinical course (5). For cases with equivocal histopathology and immunohistochemistry, polymerase chain reaction (PCR)-based studies have aided in the diagnosis of MF by detecting, with a sensitivity of 1%, the presence of a dominant clonal T-cell receptor gene rearrangement (10).

Staging and prognosis

After the diagnosis of MF is established, staging evaluations are required for determining appropriate therapy. Additionally, a patient’s prognosis can be predicted by the stage of disease. The baseline examination required is dictated by clinical examination; however, most patients will require complete blood count (CBC), screening chemistry tests, flow cytometry of the peripheral blood (to detect malignant circulating T cells), chest x-rays, and computed tomography of the abdomen and pelvis. Bone marrow biopsies are required for patients with abnormal CBC results or detectable circulating atypical cells (i.e., Sézary cells). The subsequent staging system is summarized in *Table 2* (11). While some physicians do not perform staging evaluations for early disease (stage IA), early stage patients with a detectable T-cell clone may have a worse prognosis and a higher rate of treatment failure (12).

Recently, the value of this staging system has come into question. Data from a cohort of 450 patients with MF and Sézary syndrome revealed that those with clinically positive lymph nodes with negative histology had the same prognosis as those with extensive patch disease (13). In addition, patients with extensive plaques had a worse prognosis than those with extensive patches. Finally, erythroderma and tumor stage patients had similar prognoses. If these findings are indeed confirmed, revisions in current staging and management are likely.

The long-term survival of patients with stage IA disease (diagnosis made without PCR) is similar to that of age-matched controls (14). Over 90% of patients with disease affecting <10% body surface area (BSA) and 75% of patients with disease affecting >10% BSA do not have progressive disease after treatment (14, 15). Younger patients have a favorable overall survival within any given stage (16). Large-cell transformation within 2 years of diagnosis is associated with a worse prognosis (17). Ad-

Table 2. Staging and prognosis of mycosis fungoides*

| Stage | Skin disease | Adenopathy | Lymph node pathology | Visceral involvement | Survival at 10 years |
|-------|---------------------------------------|------------|----------------------|----------------------|----------------------|
| IA | Patch/plaque (<10% BSA) | - | - | - | 100% |
| IB | Patch/plaque (>10% BSA) | - | - | - | 100% |
| IIA | Patches or plaques | + | - | - | 64% |
| IIB | Tumors | ± | - | - | 64% |
| III | Generalized erythroderma | ± | - | - | 45% |
| IVA | Patch/plaque, tumors, or erythroderma | ± | + | - | Poor |
| IVB | Patch/plaque, tumors, or erythroderma | ± | + | + | Poor |

*From reference 11. BSA indicates body surface area.

Table 3. Treatment of mycosis fungoides and Sézary syndrome

| Therapy | Reference number |
|--|------------------|
| Skin-directed therapy | |
| (early stage disease: stages IA–IIA) | |
| Topical steroids | 20 |
| Nitrogen mustard | 21 |
| Topical carmustine | 22 |
| Bexarotene gel | 23 |
| Phototherapy | |
| • PUVA | 24 |
| • Broadband ultraviolet B | |
| • Narrowband ultraviolet B (wavelength 311 nm) | 25 |
| Radiation (spot or total-body electron beam) | 26 |
| Systemic therapy | |
| (refractory early stage disease or stage IIB and above) | |
| Biologic response modifiers | |
| • Retinoids/rexinoids | 27 |
| • Interferon ± PUVA | 28, 29 |
| • Photopheresis | 30 |
| Combined modality treatment | 31 |
| Chemotherapy (single agent and multiagent) | 32–34 |
| Fusion toxin (denileukin diftitox) | 35 |
| Bone marrow transplantation | 36, 37 |
| Experimental: cytokine therapy | |

PUVA indicates psoralen + ultraviolet A.

ditionally, serum concentration of soluble IL-2 receptor correlates with tumor burden and prognosis (18).

Treatment

In the only randomized, controlled trial of active treatments for CTCL, early aggressive treatment with chemotherapy did not show a survival benefit when compared with conservative sequential therapies (19). In general, patients with early stage MF (stages IA, IB, and IIA) can be adequately treated with skin-directed therapy. In contrast, later-stage patients require systemic therapy with biologic response modifiers, photopheresis, fusion toxins, chemotherapy, or bone marrow transplantation (Table 3).

The 3 patients shown in Figures 1 through 3 were completely staged and initiated on therapy. The patient in Figure 1 had stage IA disease and has been treated with topical steroids, psoralen plus ultraviolet A, and bexarotene gel. The patient in Figure 2 had stage IIB disease and has been treated with denileukin diftitox, bexarotene capsules, interferon alfa-2a, and, most currently, combination chemotherapy. The patient in Figure 3 had Sézary syndrome and responded well to bexarotene capsules; however, he developed Hodgkin's disease with extensive liver involvement that was refractory to chemotherapy.

A CTCL clinic is held at Baylor every other Thursday in the Collins Building and is staffed by Drs. Jennifer Cather (dermatologist) and Estil Vance (oncologist and infectious disease specialist); both have extensive experience in the diagnosis and treatment of CTCL. Patients are evaluated, and treatment options are proposed to both the patient and referring doctor. Long-term follow-up is needed for patients with MF and Sézary syndrome to ensure stability of their disease and to provide surveillance for possible secondary malignancies, especially other lymphomas and lung cancer (38). All investigative procedures and therapies described in this article are available to patients through the clinic.

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