Fatal Cytotoxic Cutaneous Lymphoma Presenting as Ulcerative Psoriasis

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Background: Psoriasis is a common, nonulcerative skin disorder.

Observations: We describe 3 men recently referred to our institution for evaluation and treatment of severe, ulcerative psoriasis that ultimately was determined to be aggressive, cytotoxic, cutaneous lymphoma. Each had a history of relatively indolent, nonulcerative patches and plaques (duration, 2-45 years) that changed to ulcerated lesions; these rapidly progressed and eventuated in death.

Conclusions: The clinical characteristics of the skin lesions and the histopathologic findings form a distinct and rare presentation of cutaneous lymphoma. The initial course is similar to that of mycosis fungoides but eventuates in a highly aggressive disease with fatal outcome.

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Psoriasis is estimated to affect 2% to 3% of the population worldwide. It is typified by red, scaly, annular, and thickened skin lesions (plaques) that typically involve extensor surfaces such as elbows and knees. Although psoriasis has many subtypes, ulceration is not typical for any form of the disease.

For editorial comment see page 811

Primary cutaneous lymphoma most commonly arises from neoplastic T lymphocytes (cutaneous T-cell lymphoma [CTCL]) but also may arise from B lymphocytes and natural killer cells. Mycosis fungoides (MF) is the most common form of CTCL. Modern immunohistochemical and molecular biologic techniques have been used to develop better classification schemes for systemic and cutaneous lymphomas on the basis of cellular lineage and clinical behavior. A subset of non-MF cutaneous lymphomas that have cytotoxic phenotypes and aggressive clinical behavior recently have been recognized and are included in the World Health Organization–European Organization for Research and Treatment of Cancer classification system for cutaneous lymphoma.

We present a series of 3 patients recently treated at our institution; each had a referral diagnosis of ulcerative psoriasis that ultimately was determined to be aggressive, cytotoxic, cutaneous lymphoma. The diagnosis was difficult to establish owing to inconclusive histopathologic findings and rapidly progressive ulcerative disease that masked the underlying disease.

Methods

This study was approved by the Mayo Clinic Institutional Review Board.

The methods of the molecular genetic studies were as follows: T/c polymerase chain reaction (PCR) was performed on DNA extracted from paraffin-embedded skin and blood tissue samples. We used a single-tube multiplex assay combining 6 primers: 4 forward primers annealed to gene segments V/H92531-9 (1 consensus primer), V9, V10, and V11. Two reverse primers annealing to the J/H9253 region were used. The 5′ end of each V primer was labeled with a fluorescent dye to facilitate detection of PCR products by capillary electrophoresis. The PCR products were categorized by size into 1 of 4 nonoverlapping groups; each group allowed a range of sizes and was associated with a specific T/H9253 rearrangement. The threshold of positivity for a single (or double [biallelic]) peak population is defined as at least 3-fold greater in height than the polyclonal T-cell background in the V1-8 polyclonal T-cell distribution. The reactions were performed in duplicate, and a segment of β-globin was amplified as an internal DNA control (in fixed tissue specimens). The sensitivity of the assay was nominally 1% to 5%, although sensitivity may
be less if the polyclonal T-cell background is higher. Southern blot analysis was performed in a standard manner. High-molecular-weight DNA was digested from frozen skin tissue specimens with the EcoRI restriction endonuclease. Southern blot analysis for T-β gene locus rearrangements was performed with probes directed against the J-β1 and J-β2 regions of the T-β locus. Blots were developed with a chemiluminescent biotin–alkaline phosphatase kit (CDP-Star; New England Biolabs, Ipswich, Massachusetts) and a 2- to 4-hour exposure. Positive results were represented by new bands, seen with either probe (or both probes), that were distinct from germline and known partial digestion bands. The nominal analytic sensitivity of the Southern blot was approximately 10% of a clonal cell population within a polyclonal background (skin samples).

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of Generalized Skin Disorder, y</th>
<th>Age at Onset of Skin Ulcers, y</th>
<th>Duration of Skin Ulcers, mo</th>
<th>Prior to Onset of Ulceration</th>
<th>After Onset of Ulceration</th>
<th>After Referral</th>
<th>Cause of Death</th>
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<tr>
<td>1</td>
<td></td>
<td>52</td>
<td>9</td>
<td>Topical corticosteroids, acitretin</td>
<td>Acitretin, alfafacept, systemic corticosteroids</td>
<td>Systemic corticosteroids, interferon alfa-2a</td>
<td>Multisystem organ failure</td>
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<td></td>
<td>75</td>
<td>8</td>
<td>Topical corticosteroids, acitretin</td>
<td>Acitretin</td>
<td>Pсорalen and UV-A, gemcitabine</td>
<td>Sepsis</td>
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<tr>
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<td></td>
<td>67</td>
<td>9</td>
<td>Topical corticosteroids</td>
<td>Systemic corticosteroids, cyclosporine, methotrexate</td>
<td>Gemicitabine</td>
<td>Myocardial infarction</td>
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*a All patients were men.

### Table 2. Immunophenotypic and Molecular Genetic Findings From Skin Biopsy Specimens

<table>
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<tr>
<th>Patient</th>
<th>CD2</th>
<th>CD3</th>
<th>CD4</th>
<th>CD5</th>
<th>CD7</th>
<th>CD8</th>
<th>CD30</th>
<th>CD56</th>
<th>β-F1</th>
<th>D-1(f)</th>
<th>TIA-1</th>
<th>Gnz-B</th>
<th>EBV</th>
<th>TCR</th>
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<td>+</td>
<td>-</td>
<td>NCD</td>
</tr>
</tbody>
</table>

Abbreviations: β-F1, antibody directed against surface expression of the β chain of the αβ T-cell receptor; D-1(f), antibody directed against surface expression of the 6 chain of the γδ T-cell receptor; EBV, in situ hybridization for Epstein-Barr virus; Gnz-B, cytolytic marker for activated cytotoxic cells; NCD, no clone detected; NP, not performed; partial, less than 50% of the atypical and intraepidermal lymphoid cells were positive for the antigen tested; TCR, molecular genetic studies to identify a clonal population of T cells by using the polymerase chain reaction; TIA-1, T-cell intranuclear antigen marker for cytotoxic cells; −, absent; +, present.

Clinical characteristics of each patient are presented in Table 1. Immunophenotypic and molecular genetic findings from skin biopsy specimens are presented in Table 2. The combined clinical, immunophenotypic, and molecular genetic findings for each patient were diagnostic for primary cutaneous, cytotoxic, natural killer, or T-cell lymphoma.

**REPORT OF CASES**

A 53-year-old man was transferred from another medical center for evaluation and treatment of a severe ulcerative condition affecting the skin and mucous membranes. He reported a history of skin problems since early childhood and a diagnosis of psoriasis at age 33 years. The patient’s mother had psoriasis. His skin condition was relatively mild and responded to topical corticosteroids until a more generalized skin eruption developed 1 year before presentation. He was treated with topical corticosteroids and acitretin (25-50 mg/d), which resulted in marked improvement. About 3 to 4 months later, while the patient was still receiving acitretin, ulcers appeared within plaques on his thighs. The ulcerated plaques increased in size and distribution, and he was given a 7-week course of alefacept (15 mg/wk, administered intramuscularly) that resulted in marked improvement. Within 3 months, the condition relapsed; another course of alefacept in combination with UV-B phototherapy and acitretin was administered without benefit. The patient also received multiple doses and courses of systemic corticosteroids with variable and unsustained remission. Numerous skin biopsy samples were obtained but were considered nondiagnostic. During the next few weeks, the patient had new and larger ulcerated plaques, mucoanal ulceration, anemia, hypotenremia, leukocytosis, and hypereosinophilia. He was then transferred to our institution.

Skin examination revealed widespread ulceration with red, indurated borders (Figure 1). Seven skin biopsy specimens were obtained during his hospitalization, but 6 biopsy specimens were nondiagnostic and showed only variable mixed dermal inflammation, necrosis, and ulceration. Several specimens contained dense, granulomatosus, and eosinophilic infiltrates. One showed a superficial dermal and epidermotropic lymphoid infiltrate related to the skin.
associated with a lichenoid tissue reaction (Figure 2). The immunophenotypic and molecular genetic findings from this patient are described in Table 2.

A computed tomographic (CT) scan of the chest, abdomen, and pelvis showed no evidence of extracutaneous lymphoma, but numerous pulmonary emboli were identified. Bone marrow biopsy specimens showed slightly hypercellular marrow, but marrow involvement by lymphoma or other hematologic disorders was not observed.

Treatment with acitretin was discontinued, and the patient received dexamethasone sodium phosphate (1 mg/kg/d, administered intravenously) for 1 week, followed by interferon alfa-2a (5 million units, every other day). He also was treated with intravenous immunoglobulin in hopes of inhibiting keratinocyte apoptosis (as in toxic epidermal necrolysis). Prophylactic antibiotics and intensive wound care were administered. The patient’s condition was stable and showed clinical improvement from a cutaneous standpoint, but he decided to receive only comfort care owing to the severity and discomfort of the disease and died soon thereafter of multisystem organ failure.

CASE 2

A 77-year-old man presented with a 2-year history of a generalized skin eruption that had been diagnosed and treated as psoriasis. His initial treatment included topical corticosteroids and acitretin (25 mg/d) for a year before presentation. The patient had no family history of psoriasis. Approximately 2 months before presentation, the skin lesions began to ulcerate.

Skin examination showed generalized, indurated, and erythematous plaques. Numerous plaques were ulcerated and contained necrotic eschars (Figure 3). Three skin biopsy specimens were obtained, and each showed a lymphoid infiltrate in the superficial dermis and invading the epidermis. A lichenoid tissue reaction with numerous necrotic keratinocytes was observed (Figure 4). The immunophenotypic and molecular genetic findings of the neoplastic lymphoid cells are described in Table 2. A CT scan of the chest, abdomen, and pelvis, a peripheral blood smear, and a bone marrow biopsy specimen did not indicate the presence of extracutaneous lymphoma.

The patient underwent 10 sessions of psoralen and UV-A phototherapy without clinical improvement and was readmitted to the hospital because of sepsis. Over the ensuing weeks, the lymphoma progressed, and new ulcerated plaques developed. Two treatments with single-agent chemotherapy (gemcitabine) were administered. However, the patient had a progressive and general decline with pancytopenia; he later died of sepsis.

CASE 3

A 67-year-old man was seen in the emergency department with widespread skin ulceration; he also had fever and hypotension that were attributable to sepsis. The patient had a 20-year history of a skin eruption that had been diagnosed and treated as psoriasis; he also had a brother with psoriasis. The eruption began as erythematous patches and plaques that first involved his abdomen and slowly affected more than 80% of the body surface area. The patient had been treated previously with topical corticosteroids. Approximately 9 months before presentation, the skin lesions began to ulcerate. Moderate doses of prednisone, cyclosporine, and methotrexate were administered and resulted in mild, temporary improvement followed by a marked increase in the number, size, and distribution of ulcerating skin plaques.
Skin examination showed generalized, red-to-violeaceous plaques, many of which were ulcerated (Figure 5). Skin biopsy specimens, obtained after the onset of ulceration, were interpreted as psoriasis or were considered nondiagnostic by a pathologist at another institution. Review of the biopsy material that accompanied the referral and specimens from repeated biopsies showed a superficial dermal and epidermotropic lymphoid infiltrate associated with lichenoid tissue reaction (Figure 6). The immunophenotypic and molecular genetic findings of the neoplastic lymphoid cells are described in Table 2.

The patient initially was treated with dexamethasone (1 mg/kg/d) for approximately 1 week before starting chemotherapy with gemcitabine. The patient showed mild clinical and symptomatic improvement but experienced clinical deterioration and died of a myocardial infarction 3 weeks later.

Psoriasis affects approximately 6 to 9 million Americans. For most patients (approximately 75%), skin lesions usually present before the third decade of life. Various clinical presentations are observed, including annular, erythematous plaques on the extensor surfaces (psoriasis vulgaris), scattered, small erythematous papules (guttate psoriasis), extensive pustule formation on erythematous plaques (pustular psoriasis), generalized erythema (erythrodermic psoriasis), psoriasis of flexural skin (inverse psoriasis), scalp psoriasis, nail psoriasis, and psoriasis of the palms and soles. Environmental factors (trauma, infection, emotional stress, and medications) initiate or exacerbate psoriasis in patients with a genetic predisposition to the disease. The typical clinical disease course is characterized by chronicity. Rapid epider-
CD8+ cutaneous lymphomas that had an aggressive clinical course. The tumor cells from patient 2 in our series lacked expression of TCRs and had no clonal TCR rearrangement but were positive for CD8. Our patients also had cytotoxic T-cell lymphoma with aberrant loss of the TCR or a CD5+/EBV+ natural killer lymphoma. Although the immunophenotypic or molecular genetic features were not identical, some of these differences are likely academic. Because these subsets of cutaneous lymphoma are equally aggressive, they should be treated similarly.

Skin ulceration in cutaneous lymphoma is a well-known complication, but the mechanism for ulceration varies among lymphoma subtypes. Ulceration in MF usually occurs in tumors (not patches or plaques) and is attributable to rapid tumor growth and necrosis. Some lymphomas are prone to vascular invasion and destruction, which may result in ischemic, cutaneous necrosis. Finally, some cytotoxic lymphomas (eg, CD8+ CTCL, γδ CTCL, and natural killer lymphoma) cause ulceration through direct cytolysis of keratinocytes by neoplastic lymphocytes. The mechanism of skin necrosis and ulceration is similar to that of graft-vs-host disease, Steven-Johnson syndrome, lichen planus, and lupus erythematosus. Routine histopathologic analyses of skin biopsy specimens from patients with these disorders show a lichenoid tissue reaction.

Large-cell transformation of MF is a well-described phenomenon in which the large cells (usually CD30+) constitute more than 25% of the infiltrate or form microscopic nodules. The incidence of transformation in MF is variable (occurring in 8%-55% of cases). Various environmental and genetic factors have been implicated...
in the pathogenesis of transformation. Clinical features associated with a poor prognosis in large-cell transformation of MF include early transformation (<2 years after the initial diagnosis of MF), advanced clinical stage at time of transformation (stage IIB-IV), older age (≥60 years), and extracutaneous invasion. Several reports in the literature describe patients with long histories of atopic dermatitis and psoriasis who have CD30+ cutaneous and nodal lymphoma occurring after initiation of systemic therapies (cyclosporine, methotrexate, oral retinoids). A proposed mechanism for lymphoma development in these cases implicates chronic antigenic stimulation from bacterial colonization in conjunction with iatrogenic immunosuppression that fosters persistent and malignant transformation of T-cell clones. The effect of systemic retinoids or immunosuppressive agents on the initiation or exacerbation of cytotoxic lymphoma is unknown. Other than the chronic use of topical corticosteroids, none of our patients received systemic immunosuppressive agents before the aggressive, ulcerative phase of their illness developed. Moreover, no large-cell transformation was observed in the biopsy specimens from any of our patients.

For our 3 patients, the precise characterization and cause of the earlier, nonulcerative skin eruption cannot be known because skin biopsy specimens were not obtained, nor did we clinically evaluate the skin eruption during this period. The nonulcerative disease may have been psoriasis or eczema, and the acute onset of ulcerative plaques would have occurred after acquisition of an aggressive cutaneous lymphoma. Alternatively, the skin disease may initially have been MF that later transformed to a highly unusual, cytotoxic phenotype that resulted in epithelial destruction and ulceration. Both theories are plausible, but the literature lacks well-documented evidence of either scenario.

CONCLUSION

The clinical presentation, disease course, and histologic and immunophenotypic changes of the 3 patients in this series were strikingly similar to each other but markedly distinct from psoriasis or typical MF. Common features among our 3 patients are as follows:

- Long duration (years) of an indolent, chronic, nonulcerative, limited, or generalized scaly dermatitis or psoriasis-like skin condition
- A short period (months) of a rapidly progressive, ulcerative skin disease
- Histopathologic examination showed a lichenoid tissue reaction pattern
- Immunophenotypic and molecular genetic findings indicated a primary, cutaneous, cytotoxic (T-cell or natural killer–cell) lymphoma
- Abbreviated clinical course culminated in death within 9 months of development of skin ulcerations

The paramount lesson from these cases is that psoriasis vulgaris does not ulcerate. We strongly believe that
Figure 5. Clinical photograph of patient 3 shows extensive red-to-purple, necrotic, and ulcerated patches and plaques on the back.

Figure 6. Photomicrographs of an abdominal lesion biopsy (patient 3). A, Dense, superficial, dermal, and epidermotropic lymphoid infiltrate; B, marked lichenoid tissue reaction with numerous necrotic keratinocytes (hematoxylin-eosin, original magnifications ×100 and ×200, respectively). C-E, Immunoreactivity of neoplastic and intraepidermal lymphoid cells (original magnification ×200). C, Positive reaction to anti-CD5 antibodies. D, Positive reaction to anti–TIA-1 (T-cell intranuclear antigen marker) antibodies. E, Negative reaction to anti–β-F1 antibodies (directed against surface expression of the αβ T-cell receptor).
all clinicians should be aware of the clinicopathologic presentation of this disease. Aggressive, cytotoxic CTCL should be in the differential diagnosis of patients who present with ulcerated plaques or skin lesions that are atypical for psoriasis. In presumed cases of psoriasis that are progressive, unresponsive to conventional treatment, or ulcerative, patients should undergo biopsy. Moreover, a potent immunosuppressive agent should be used only for patients with biopsy-proven psoriasis. Careful correlation of clinical and pathologic findings, repeated biopsies, and extended immunophenotypic analysis may be required to avoid missed and delayed diagnoses of cytotoxic cutaneous lymphoma.

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Author Contributions: Dr Weenig had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Weenig, Comfere, Gibson, and Davis. Acquisition of data: Weenig and Alonso-Llamazares. Analysis and interpretation of data: Weenig, Comfere, Gibson, Alonso-Llamazares, Davis, Pittelkow, and el-Azhary. Drafting of the manuscript: Weenig and el-Azhary. Critical revision of the manuscript for important intellectual content: Weenig, Comfere, Gibson, Alonso-Llamazares, Davis, Pittelkow, and el-Azhary. Administrative, technical, and material support: Weenig and Davis. Study supervision: Alonso-Llamazares.

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