Unusual Cutaneous Manifestation of Angiocentric T-Cell Lymphoma: A Case Report

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Angiocentric T-cell lymphoma may clinically present with a broad variety of cutaneous manifestations, including papules, nodules, and ulcerated tumors, and may mimic cutaneous vasculitis and Wegener granulomatosis. Histologic diagnosis of angiocentric T-cell lymphoma also may present a challenge because of variations in the degree of cellular infiltrate and cellular atypia. The correct diagnosis is critical because of the importance of choosing the correct therapeutic modality—chemotherapy or x-ray radiation. We report a case of angiocentric T-cell lymphoma with extensive necrotic facial ulcers that responded to treatment with fludarabine, cyclophosphamide, and prednisone.

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Angiocentric T-cell lymphoma is a systemic disease with a broad variety of cutaneous manifestations such as papules, nodules, and ulcerated tumors.[1] Several other cutaneous manifestations of the disease have been reported, including a case masquerading as cutaneous vasculitis with an initial biopsy result consistent with polyarteritis nodosa[2] and a case that presented as a destructive centrofacial process mimicking Wegener granulomatosis.[3] Nasal and nasal-type extranodal natural killer (NK) cell/T-cell lymphoma (previously designated as lethal midline granuloma[4]) is closely related but affects the skin as a secondary process rather than a primary process,[5] either extending from the primary mid facial destructive tumor (nasal lymphoma) or from the tumor located outside the nasal cavity (nasal-type lymphoma). The diagnosis is critical because each disease responds differently to the therapeutic modalities of chemotherapy and x-ray radiation.

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We present the case of a 64-year-old woman who developed several polymorphous cutaneous lesions with nonspecific pathology at the onset of her disease and subsequently developed necrotic facial ulcers with a pathology consistent with angiocentric T-cell lymphoma.

Case Report

A 64-year-old white woman, previously hospitalized for acute respiratory failure with acute respiratory distress syndrome following coxsackie B viral infection, developed a polymorphic papular eruption on her trunk and extremities. Three skin lesion biopsies were performed: a right leg specimen that showed lymphocytic infiltrate, a right shoulder specimen that showed interface dermatitis, and a right forearm specimen that showed lymphocytic vasculitis. It was thought that the patient had vasculitis secondary to coxsackie B virus, and she was started on cyclophosphamide in addition to prednisone.

The patient subsequently was found to have hemolytic anemia and was undergoing a diagnostic workup when she suddenly developed hemorrhagic necrotic areas on the face and right earlobe. Results of the first bone marrow biopsy were suggestive of T-cell clonality; results of the second biopsy were suggestive of T-cell lymphoproliferative disease and possibly T-cell lymphoma. The biopsy result of the mediastinal lymph node was negative for tumor. Six weeks later, the patient developed new cutaneous findings on her face that were thought to be due to exogenous pressure from her oxygen mask. Results of a physical examination performed at that time revealed a middle-aged woman who was extremely weak and unable to get out of bed. Results of a skin examination revealed sharply demarcated, geometrically outlined necrotic ulcers with hemorrhagic crusts on the cheeks bilaterally, the tip and root of the nose, the upper lip, and the right earlobe (Figure 1). In addition, the patient's upper and lower extremities had several diffusely distributed erythematous papules.

At that time, skin biopsies were performed: specimens from the right cheek and the root of the nose.

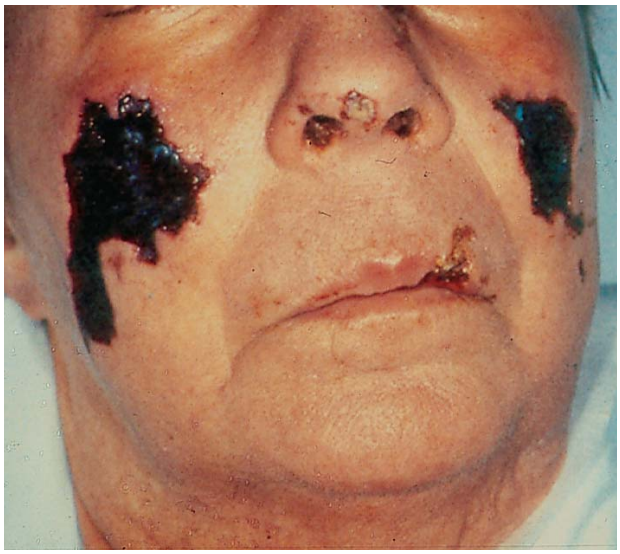

Figure 1. Sharply demarcated necrotic ulcers on the face.

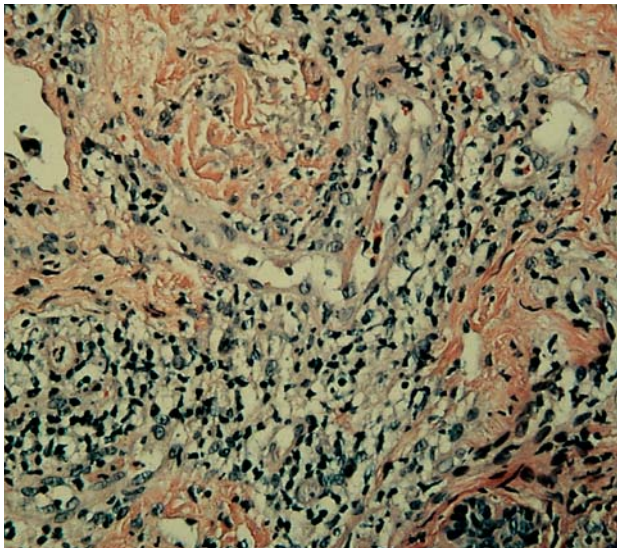

Figure 2. A brisk, atypical, angiocentric T-cell infiltrate with vascular channels lined by predominant endothelial cells (H&E, original magnification ×200).

The biopsy result of the cheek lesion demonstrated brisk, atypical, angiocentric T-cell infiltrate with vascular channels lined by prominent endothelial cells, which was consistent with involvement by peripheral T-cell lymphoma (Figure 2). A biopsy performed on the nose lesion had similar findings, as well as extensive necrosis and ulceration of the superficial dermis and epidermis.

Section immunoassay test results indicated the dominance of an atypical perivascular and intramural $CD3^+$ T-cell infiltrate, which was $CD30^-$ (Figure 3). CD31 highlighted the endothelial cells and the angiocentric nature of the infiltrate. Rare B cells were shown by CD20 immunostaining.

Molecular genetic analysis of the patient's leukocytes by polymerase chain reaction for the T-cell receptor-γ gene rearrangement revealed a monoclonal distribution of these rearrangements. These results were consistent with the presence of a monoclonal population of neoplastic T cells, and a diagnosis of angiocentric T-cell lymphoma was made.

The patient was started on chemotherapy with fludarabine, cyclophosphamide, and prednisone. To date, she has completed 4 cycles of chemotherapy, and her pulmonary symptoms and fatigue improved. The patient's facial ulcers were treated with aluminum acetate soaks and mupirocin nasal ointment, with complete healing. Residual depressed scars can be seen on her cheeks and nose. At her last follow-up visit, she had no new cutaneous lesions, and her T-cell lymphoma was stable.

Comment

Angiocentric lymphomas are a heterogenous spectrum of lymphoproliferative malignancies that share a particular histologic characteristic (ie, an angiocentric growth pattern). They include a variety of T, B, and NK cell–derived lymphomas characterized by different clinical and pathologic features and prognosis.[1] Initially, the term *angiocentric lymphoma* was used to refer to NK cell and NK cell–like T-cell lymphomas that show a prominent angiocentric growth pattern. Angiocentric lymphomas are characterized by neoplastic lymphocytes, which tend to infiltrate blood vessel walls and invade other organs. Systemic symptoms usually are observed when pulmonary and central nervous systems are involved.

The cutaneous findings in angiocentric T-cell lymphomas are heterogeneous, with subcutaneous or dermal nodules being the most common morphologies. However, lesions ranging from papules to ulcerated nodules have been reported.[1] The histologic diagnosis of angiocentric T-cell lymphoma may represent a challenge. The histologic manifestations vary in the degree of cellular infiltrate and cellular atypia, thus angiocentric T-cell lymphoma can be confused with a variety of benign and neoplastic disorders. In addition, the vascular damage leads to vascular compromise, which may lead to tissue anoxia and cause cutaneous necrosis, as in our patient—a condition that can potentially obscure the microscopic picture. Vascular damage from the neoplastic infiltrate is evidenced by fibrin deposition in the vessel walls or lumens, intimal fibrosis, and perivascular fibrosis.

The proportion of neoplastic cells in the infiltrate is highly variable. Some of the infiltrate are

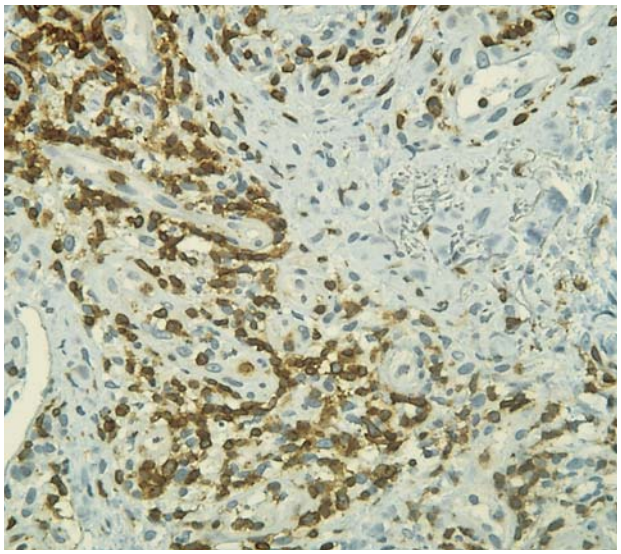

Figure 3. CD3+ immunostain identifies the majority of angiocentric mononuclear cells (H&E, original magnification ×200).

impossible to diagnose histologically because of a subtle cytologic atypia of the neoplastic cells. Most commonly, the neoplastic cells demonstrate medium nuclei with rounded or irregular borders. Rarely, true cerebriform morphology is encountered.

Clonal Epstein-Barr virus genomic integration appears to play an important role in the pathogenesis of some angiocentric lymphomas, especially those of NK cells or NK cell–like lineage. In situ hybridization or immunoperoxidase staining for Epstein-Barr virus genome or proteins can be employed to seek evidence of Epstein-Barr virus integration.

The histologic differential diagnosis is broad and includes both neoplastic and benign disorders.[6] If there are few neoplastic cells, the infiltrate can be confused with a plain perivascular infiltrate or dermatitis; this was the case in the initial biopsy result of the lesion specimens from the extremities of our patient. If there is a dense lymphocytic infiltrate, the differential diagnosis will include pityriasis lichenoides and lymphocytic vasculitis associated with pernio. The finding of atypical lymphocytes and molecular studies both aid in the diagnosis of a neoplastic process.

Among the neoplastic disorders, lymphomatoid papulosis most commonly demonstrates angiocentric distribution that may simulate angiocentric T-cell lymphoma. Lymphomatoid papulosis, however, is characterized by involvement of superficial dermis and epidermis and by a wedge-shaped infiltrate that stains CD30+. Various forms of epidermotrophic cutaneous T-cell lymphoma, including mycosis fungoides, rarely may display angiocentricity. However, the predominant pattern in these cases is epidermotropism; this is in contrast to angiocentric T-cell lymphoma, in which epidermotropism is usually minimal.

Angiocentric lymphoma also may be confused with angiotrophic lymphoma. The distinguishing feature of angiotrophic lymphoma, which is an intravascular lymphoma, is that the neoplastic cells are located within vessel lumens rather than within vessel walls; in addition, most angiotrophic lymphomas are of B-cell lineage.

Pulmonary and central nervous system diseases are common and can precede or follow cutaneous lesions. Because of systemic involvement, the prognosis of angiocentric lymphoma is guarded, with 5-year survival rates of less than 50% in some variants.[7] Treatment with systemic chemotherapeutic agents is indicated.

Conclusion

Angiocentric T-cell lymphoma may present with a variety of cutaneous manifestations. We presented this case because of its diagnostic challenge, including several initial nonspecific skin biopsy results of polymorphic cutaneous lesions, followed by development of unusual necrotic facial ulcers with pathologic, immunohistochemical, and polymerase chain reaction findings diagnostic of angiocentric T-cell lymphoma.

REFERENCES

1. Nathukam Y, Warnke RA. Angiocentric lymphomas. *Semin Diagn Pathol*. 2001;18:67-77.
2. Thomas R, Vuitch F, Lakhanpal S. Angiocentric T cell lymphoma masquerading as cutaneous vasculitis. *J Rheumatol*. 1994;21:760-762.
3. Vera Llao R, Girons Bonells J, Serrano Pinol T, et al. Peripheral centrofacial T lymphoma. *Acta Otorrinolaringologica*. 1996;47:239-242.
4. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. *Blood*. 1994;84:1361-1392.
5. Kakihara T, Imai C, Hotta H, et al. Centrofacial malignant T cell lymphoma exhibiting recurrent fever and skin ulcers in a 3-year-old girl. *Pediatr Hematol Oncol*. 2002;19:575-580.
6. LeBoit PE, McCalmont TH. Cutaneous lymphomas and leukemias. In: Elder D, Elenitsas R, Jaworsky C, et al, eds. *Lever's Histopathology of the Skin*. Philadelphia, Pa: Lippincott-Raven; 1997:836-837.
7. James WD, Odom RB, Katzenstein AL. Cutaneous manifestations of lymphomatoid granulomatosis: report of 44 cases and review of the literature. *Arch Dermatol*. 1981;117:196-202.