CD8⁺ Epidermotropic Cytotoxic T-Cell Lymphoma With Peripheral Blood and Central Nervous System Involvement

Camille E. Introcaso, MD; Ellen J. Kim, MD; Jennifer Gardner, MD; Jacqueline M. Junkins-Hopkins, MD; Carmela C. Vittorio, MD; Alain H. Rook, MD

Background: Most cutaneous T-cell lymphomas demonstrate a malignant population with a CD4⁺/CD8⁻ phenotype. In rare cases, CD8⁺/CD4⁻ phenotypes have been described based on immunostaining of skin specimens. Although some CD8⁺ lymphomas have an indolent course, others, such as CD8⁺ epidermotropic cytotoxic T-cell lymphomas, are typically more aggressive. To our knowledge, involvement of peripheral blood or cerebrospinal fluid with a malignant population of CD8⁺ cells demonstrated by flow cytometry and T-cell receptor gene rearrangement has not been previously described.

Observations: We describe a patient with a CD8⁺ cutaneous T-cell lymphoma with an initially indolent course and early stage diagnosed on the basis of a skin biopsy specimen. However, when flow cytometry was performed looking specifically at CD8⁺/CD4⁻ cells in the peripheral blood and cerebrospinal fluid, a malignant population of CD8⁺/CD4⁻/CD26⁻/CD7⁻ cells was discovered.

Conclusions: It is important for prognosis and treatment to be able to identify CD8⁺ epidermotropic cytotoxic T-cell lymphoma and separate it from other relatively indolent CD8⁺ lymphomas. Furthermore, detection of an abnormal CD8⁺/CD26⁻/CD7⁻ T-cell population within the peripheral blood has important prognostic and therapeutic implications. The use of flow cytometry looking for abnormal CD8⁺ populations in the peripheral blood or cerebrospinal fluid can assist with this critical information.

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Author Affiliations:
Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia.
During the next year, the patient’s skin lesions improved, but she continued to develop new lesions despite therapy with oral bexarotene, 225 mg/d, initially in combination with topical nitrogen mustard, 0.02%, and subsequently psoralen–UV-A light 2 to 3 times per week. Because of recalcitrant disease, skin biopsies were performed again, and the specimens demonstrated large, epidermotropic, atypical CD8\(^+\) cells (Figure 1 and Figure 2). The results of testing for human immunodeficiency viruses 1 and 2 and human T-cell lymphotropic virus 1 with enzyme-linked immunosorbent assay were negative, and positron emission tomography and computed tomography revealed no abnormalities. Flow cytometric analysis was repeated, this time with a specific request to the laboratory to examine the CD8\(^+\) cells. The total white blood cell count was 44,000/µL (to convert to value \(\times 10^9/L\), multiply by 0.001) with 22% lymphocytes on differential. The CD4:CD8 ratio was again decreased at 0.7:1, and a discrete population of CD8\(^+\)/CD26\(^-\) cells composed 39% of the total peripheral blood lymphocytes, which had a dominant T-cell receptor gene rearrangement identical to that in her skin. No significant populations of CD8\(^+\)/CD7\(^-\), CD4\(^+\)/CD26\(^-\), or CD4\(^+\)/CD7\(^-\) cells were found.

Based on the presumption that these CD8\(^+\)/CD26\(^-\) cells represented leukemic involvement, the patient was administered extracorporeal photopheresis. Because the patient continued to develop new lesions, oral bexarotene and psoralen–UV-A therapies were discontinued and interferon alfa and topical nitrogen mustard, 0.03%, therapies were started. The active lesions became less inflammatory after a short course of local electron beam radiation. The patient was stable for approximately 6 months; however, she then developed sudden onset of headache and neck pain. A lumbar puncture demonstrated 61 leukocytes per deciliter of cerebrospinal fluid (CSF), with 96% of these being lymphocytes. Flow cytometric analysis of these lymphocytes, again with specific gating on CD8\(^+\) cells, demonstrated discrete populations of cells that were CD8\(^+\)/CD7\(^-\) (61% of the total lymphocytes) and CD8\(^+\)/CD26\(^-\) (67% of the total lymphocytes). Molecular analysis revealed that she had a T-cell clonal population in her skin and blood. These results combined with the patient’s clinical picture of meningismus were suggestive of CTCL that involved the central nervous system.

**COMMENT**

Four distinct subtypes of CD8\(^+\) CTCLs have been identified, the first of which has been well defined and is designated as primary cutaneous CD8\(^+\) epidermotropic cytotoxic T-cell lymphoma in the most recent World Health Organization–European Organisation for Research and Treatment of Cancer cutaneous lymphoma classification scheme.\(^3\)\(^6\) As the name suggests, this subtype exhibits marked epidermotropism on histopathologic analysis. It has a poor outcome and can involve the central nervous system, lungs, testis, and oral mucosa. The histopathologic features and course of our patient’s disease place her in this category. The other 3 subtypes of CD8\(^+\) lymphomas recognized by the World Health Organization–European Organization for Research and Treatment of Cancer classification include subcutaneous panniculitic-like T-cell lymphoma; cutaneous CD8\(^+\) lymphomas associated with congenital or acquired immunodeficiencies, including human immunodeficiency virus; and a heterogeneous category that includes CD8\(^+\) variants of other well-defined CTCLs, including mycosis fungoides and anaplastic large T-cell lymphoma. This last group of CD8\(^+\) lymphomas has been described to have a similar clinical course as the CD4\(^+\) counterparts of each entity.\(^3\)

Figure 1. Skin biopsy specimen demonstrating large, atypical lymphocytes with epidermotropism (hematoxylin-eosin, original magnification \(\times 20\)).

Figure 2. Higher magnification of large, atypical lymphocytes demonstrating epidermotropism (hematoxylin-eosin, original magnification \(\times 40\)).
Previous reports of CD8+ CTCLs have determined that the malignant cell is CD8+ based on immunophenotyping and PCR testing for T-cell gene rearrangements in skin biopsy specimens. In our patient, the presence of a clonal population of T cells was also confirmed by flow cytometry and T-cell gene rearrangement PCR to be in the peripheral blood and eventually in the CSF. It is a critical finding that the malignant CD8+ cells demonstrated loss of the same T-cell markers CD7 and CD26 that have been previously described as absent in CD4+ CTCLs.7,8 The ability to measure loss of CD26 and CD7 represents a powerful tool for diagnosis and monitoring of peripheral blood involvement in these patients, many of whom we know will eventually have aggressive disease. Identifying patients who have peripheral blood involvement allows physicians to make interventions with appropriate therapy at an earlier point. For example, institution of photopheresis, referral to clinical trials, or evaluation for a stem cell transplantation may all be undertaken at an earlier point if a patient is known to have a significant burden of peripheral blood disease or visceral involvement. 

A CD8+ malignant neoplasm may be suggested by the patient’s histopathologic findings or an inverted CD4:CD8 ratio on histopathologic analysis or peripheral blood examination. If so, it is important to request that the gating on the flow cytometry be performed specifically on CD8+ cells so that any abnormal populations can be detected. In our patient, the diagnosis of peripheral blood involvement may have been delayed because of an initial flow cytometry that focused only on CD4+ populations that found no CD7− or CD26− cells.

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Correspondence: Camille E. Introcaso, MD, Department of Dermatology, Hospital of the University of Pennsylvania, 2 Maloney Bldg, 3400 Spruce St, Philadelphia, PA 19104 (camille.introcaso@uphs.upenn.edu).

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REFERENCES