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# Denileukin Diftitox for the Treatment of Panniculitic Lymphoma

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

## REPORT OF A CASE

A 24-year-old white woman presented with a 9-month history of proximal extremity nodules, associated with fevers and arthralgias, that had only a partial response to a combination of oral prednisone, topical betamethasone ointment, and topical calcipotriene ointment.

Examination revealed a healthy-appearing woman with a low-grade fever. There were annular and polycyclic eroded plaques and firm subcutaneous nodules on her proximal arms and dusky red, atrophic plaques on her right thigh and the middle of her back (**Figure 1A**). Laboratory evaluation revealed a microcytic anemia (hemoglobin, 11.2 g/dL; mean corpuscular volume, 77 fL) and normal liver function test results. Results of several skin biopsies showed histological and immunophenotypic features of subcutaneous panniculitic T-cell lymphoma (**Figure 2A and B**).

A positron emission tomographic scan showed multiple foci of intense fludeoxyglucose F 18 uptake superficially within the upper extremities and proximal right lower extremity consistent with the cutaneous T-cell malignancy, without extracutaneous disease (**Figure 3A**).

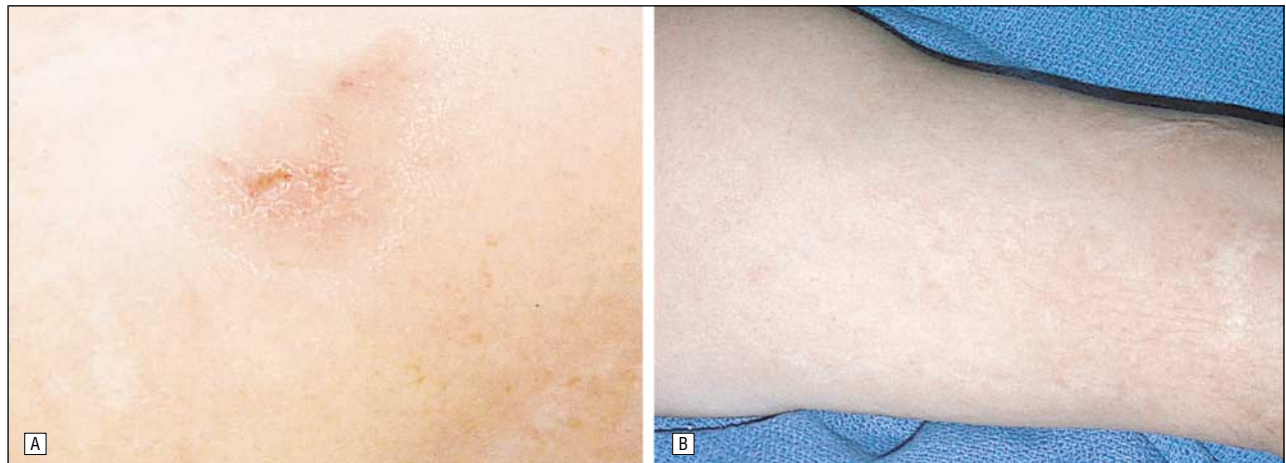
She initially responded to bexarotene (Targretin; Ligand Pharmaceuticals Inc, San Diego, Calif) (150 mg/d) and interferon alfa ( $1.8 \times 10^6$  U, 3 times weekly). However, within 2 months of initiating these therapies, her disease had progressed rapidly with an increase in size, number, and degree of infiltration of the lesions and worsening of her constitutional symptoms with increased fatigue and low-grade fevers. She was prescribed prednisone (15 mg/d orally).

## THERAPEUTIC CHALLENGE

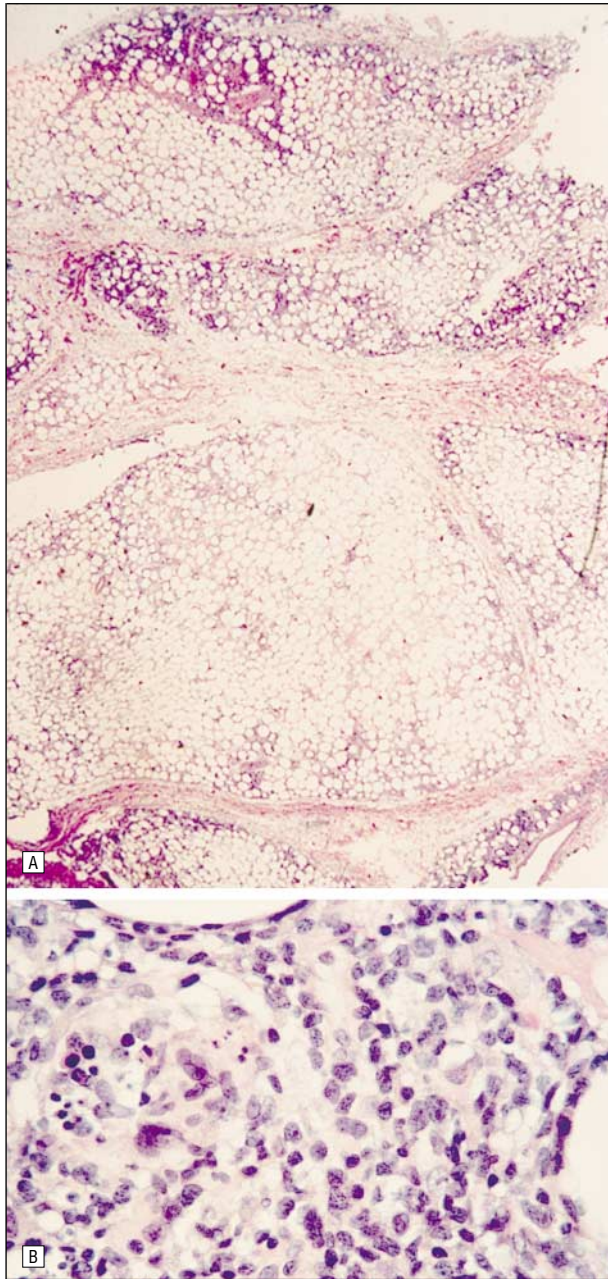
The poor prognosis of rapidly progressive subcutaneous panniculitic T-cell lymphoma as well as the proven therapeutic efficacy of denileukin diftitox (Ontak; Ligand Pharmaceuticals Inc) for the treatment of cutaneous T-cell lymphoma (CTCL)<sup>1</sup> prompted us to evaluate its potential benefit in subcutaneous panniculitic T-cell lymphoma.

## SOLUTION

Five cycles of intravenous denileukin diftitox (9  $\mu$ g/kg daily for 5 days [1 cycle]) were administered. Clinical

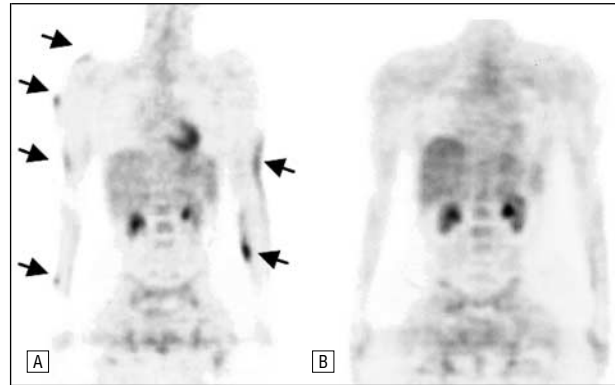


**Figure 1.** A, Pretreatment clinical picture showing skin lesions on right arm demonstrating a dusky red, annular eroded plaque overlying a subcutaneous nodule. B, Posttreatment clinical picture showing resolution of the erythema with residual subcutaneous tissue atrophy.



**Figure 2.** A, Scanning-power view of a biopsy specimen taken from a right thigh nodule prior to therapy demonstrating a dense lobular atypical lymphoid infiltrate with areas of coagulation necrosis (hematoxylin-eosin, original magnification  $\times 20$ ). B, Intermediate-power view of the lymphoid infiltrate showing a pleomorphic population of intermediate to large lymphocytes. There is rimming of adipocytes by atypical lymphocytes, emperipoiesis, and karyorrhexis (hematoxylin-eosin, original magnification  $\times 400$ ).

remission, with resolution of all cutaneous disease and constitutional symptoms, was achieved 2 weeks after the completion of the third cycle of denileukin diftitox (Figure 1B). A repeated positron emission tomographic scan confirmed the resolution of cutaneous disease (Figure 3B). At that time, prednisone was tapered off prior to the fourth cycle. Nine months after completion of denileukin diftitox therapy, the patient remains in complete remission.



**Figure 3.** A, Pretreatment positron emission tomographic scan (July 28, 2000) demonstrating multiple foci of intense fludeoxyglucose F 18 uptake noted superficially within both upper extremities consistent with the patient's known subcutaneous lymphoma. B, Positron emission tomographic scan after 3 cycles of denileukin diftitox (February 1, 2001) showing resolution of the initial findings of increased fludeoxyglucose F 18 uptake in the upper extremities.

### COMMENT

Subcutaneous panniculitic T-cell lymphoma is a rare form of T-cell lymphoma characterized by primary involvement of the subcutaneous fat in a manner that mimics panniculitis.<sup>2</sup> It typically presents with tan-to-red, deep-seated nodules, particularly on the extremities, with systemic complaints of low-grade fever and weight loss.<sup>3,4</sup>

The behavior of subcutaneous panniculitic T-cell lymphoma is generally considered to follow 1 of 2 clinical courses: aggressive disease associated with a hemophagocytic syndrome or indolent disease with recurrent, self-healing lesions.<sup>5</sup> The hemophagocytic syndrome is characterized by florid hemophagocytosis, thought to be triggered by a phagocytosis-inducing factor secreted by the neoplastic T cells.<sup>4</sup> Clinically, this is manifested as pancytopenia and hyperbilirubinemia, rapidly terminating in death secondary to either bleeding or infection.<sup>6</sup>

Treatments that have been used in the past include systemic chemotherapy,<sup>5,7,8</sup> radiotherapy,<sup>5</sup> high-dose chemoradiotherapy with stem cell support,<sup>9</sup> and limb amputation.<sup>10</sup> The results have ranged from a fulminant course with hemophagocytic syndrome and death to complete and sustained remission. Unfortunately, there has been no comprehensive study to determine clinicohistopathological features that may predict progression to hemophagocytic syndrome. It is thought, however, that the presence of fever, weight loss, cytopenia, involvement of multiple sites, and hemophagocytosis at the time of diagnosis may portend a more aggressive course and a poor clinical outcome.<sup>8</sup>

Denileukin diftitox is a recombinant fusion protein that combines human interleukin 2 and diphtheria toxin.<sup>11</sup> When the gene is expressed in *Escherichia coli*, it results in the production of a polypeptide chain with the capacity to bind to the human interleukin 2 receptor (IL-2R) on T cells and to inhibit protein synthesis upon internalization.<sup>12</sup> The human IL-2R exists in 3 forms: low, intermediate, and high affinity. Only the intermediate and high-affinity forms will allow endocytosis of the bound ligand to occur. Cells that exhibit the high-affinity IL-2R

appear to be approximately 1 log more sensitive to the cytotoxic effects of denileukin diftitox than are the cells expressing the intermediate affinity receptor.<sup>13</sup>

Expression of the IL-2R in involved tissue has been observed in up to 75% of cases of CTCL using immunohistochemical techniques.<sup>14</sup> Nevertheless, a great degree of variability has been observed from lesion to lesion within individual patients and from patient to patient, depending upon the particular reagents used. Furthermore, no clear correlation has been observed between IL-2R expression and responsiveness of CTCL patients treated with denileukin diftitox.

A recent phase 3 trial found that 30% of the 71 patients with CTCL treated with denileukin diftitox had an objective response (20% partial response and 10% complete response).<sup>1</sup> Some patients demonstrated marked variability in IL-2R expression among different lesions, yet had significant responses to treatment. The study concluded that denileukin diftitox is a "useful and important" agent in the treatment of patients whose CTCL is "persistent or recurrent despite other therapeutic interventions." Furthermore, it was found to have a relatively benign side effect profile with less myelosuppression compared with traditional chemotherapeutic regimens.<sup>1</sup>

In contrast to CTCL, expression of the IL-2R in panniculitic T-cell lymphoma tumors has not been quantified. Since this is a disorder of malignant T cells with an activated phenotype, we hypothesized that denileukin diftitox would have the ability to kill the malignant T cells of subcutaneous panniculitic T-cell lymphoma by a similar mechanism. Moreover, we believe that denileukin diftitox may be able to exert its cytotoxic effect without activating the cytokine storm that results from the secretion of the phagocytosis-inducing factor that contributes to the hemophagocytic syndrome.

Since the report of our patient, we have become aware of 3 additional patients with subcutaneous panniculitic T-cell lymphoma in whom other treatments failed but who have responded to treatment with denileukin diftitox (A.H.R., unpublished data, 2001). These observations support our therapeutic concept that denileukin diftitox is an effective, relatively nontoxic therapy for panniculitic T-cell lymphoma that may not induce hemophagocytic syndrome and should be considered as an acceptable first-line therapy for this disease.

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## Submissions

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017. Reprints are not available.

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