**OBSERVATION**

A Case of Refractory Sézary Syndrome With Large-Cell Transformation Responsive to Brentuximab Vedotin

Brentuximab vedotin is a CD30-directed antibody/drug conjugate recently approved for the treatment of relapsed Hodgkin lymphoma (HL) and systemic anaplastic large-cell lymphoma (ALCL). Given that CD30 is variably expressed in mycosis fungoides (MF) and Sézary syndrome (SS), brentuximab vedotin is a promising treatment option for these cutaneous neoplasms. Initial studies have confirmed its clinical activity in refractory cases.

**Report of a Case |** An 85-year-old white woman with early dementia presented with 6 months of fatigue, weight loss, and diffuse pruritic violaceous patches and plaques (Figure 1A). Findings from lymph node examination were unremarkable. Biopsies of a patch and plaque on the back revealed a dense bandlike infiltrate of atypical lymphocytes in the dermis with large and irregular forms (Figure 2A). Atypical lymphocytes extended into the epidermis arranged along the dermal-epidermal junction and within the Pautrier microabscesses (Figure 2B). Immunohistochemical staining characterized the lymphocytic population as CD3⁺ T-lymphocytes with a predominance of CD4⁺ over CD8⁺ cells. Expression of CD7 was decreased. Loose aggregates of enlarged dermal lymphocytes, making up approximately 25% of the lymphoid infiltrate, showed CD30 positivity (Figure 2C). Anaplastic lymphoma kinase staining was negative. A complete blood cell count was within normal limits. The lactate dehydrogenase level was normal at 522 U/L.

Peripheral flow cytometry revealed immunophenotypically abnormal CD4⁺ T-cells with reduced CD2 and CD3 expres-
sion and loss of CD7 making up 42% of the total lymphocytes. These findings were suggestive of stage IVA (T3B2) SS with large-cell transformation.

The patient was started on bexarotene treatment but experienced progressive cognitive decline after 4 weeks. Her disease continued to progress rapidly with enlarging pruritic plaques on her trunk and disfiguring confluent nodules on her face causing leonine facies (Figure 1B). A 2-month trial of narrowband UV-B phototherapy with topical steroids and several local radiation treatments were ineffective. Two months of alemtuzumab therapy resulted in cytomegalovirus viremia without improvement in skin lesions.

Since a significant proportion of the lymphoid infiltrate expressed CD30, brentuximab vedotin therapy was approved and initiated at a dose of 1.2 mg/kg followed by 1.4 mg/kg every 3 weeks. After 5 cycles, regression of nodules and plaques was observed, and the patient reported significantly decreased pruritus (Figure 1C). She denied any adverse effects, including nausea and neuropathy. Of note, she developed a pink crateriform tumor with central ulceration during treatment, which was found to be consistent with tumor stage MF. Immunohistochemical staining of this tumor was positive for CD3 and CD4 with rare large cells positive for CD30.

Discussion | Brentuximab vedotin demonstrates antitumor activity against malignant cell types expressing CD30 in relapsed HL and systemic ALCL. In addition to HL and ALCL, the CD30 cell surface receptor is expressed in cutaneous neoplasms including lymphomatoid papulosis and MF/SS. In MF/SS, CD30 expression is associated with late-stage disease and large-cell transformation, but variable expression of CD30 can occur at all stages. Therefore, targeting CD30 with use of brentuximab represents a promising therapeutic strategy in MF/SS.

Clinical trials are ongoing to determine the efficacy of brentuximab in MF/SS. The results of a pilot study of 19 patients suggest that brentuximab has significant clinical activity in patients with MF/SS across all levels of CD30 expression. A recently presented case series described 1 patient with CD30+ MF who showed a complete response to brentuximab vedotin. To our knowledge, this is the first case report of successful brentuximab vedotin use in a patient with SS with large-cell transformation and CD30 positivity. Our patient developed a solitary tumor during treatment that was mostly CD30−, indicating that CD30+ cells were effectively targeted during brentuximab treatment. Further studies are needed to elucidate the role of brentuximab therapy in MF/SS and other cutaneous CD30+ lymphoproliferative disorders.

Kristen Corey, BS
Deborah Cook, MD
Jessica Bekker, MD
Emiliano Mugnaini, MD, PhD
Julie H. Lin, MD

Author Affiliations: University of Massachusetts Medical School, Worcester (Corey); Department of Pathology, University of Vermont College of Medicine, Burlington (Cook, Bekker); Division of Hematology/Oncology, University of Vermont College of Medicine, Burlington (Mugnaini); Division of Dermatology, University of Vermont College of Medicine, Burlington (Lin).

Corresponding Author: Julie H. Lin, MD, Division of Dermatology, University of Vermont College of Medicine, 111 Colchester Ave, Burlington, VT 05401 (Julie.Lin@vtmednet.org).
Laser Recall Dermatitis

Chemotherapy-induced recall dermatitis is a phenomenon whereby the administration of a chemotherapy agent induces an inflammatory reaction at sites injured previously, days, months, or even years earlier. Radiation recall dermatitis, where the inflammatory reaction appears at a previously irradiated site, and reactivation of UV light–induced erythema after methotrexate therapy are the prototypes of recall phenomena. A few cases of chemotherapy recall phenomenon on a site of drug extravasation and on a previously scalded skin were described. The pathogenic mechanism of the recall phenomenon is not exclusive for chemotherapy drugs and may also be induced by tuberculostatic drugs, antibiotics, and simvastatin.

Report of a Case | A man in his 30s, evaluated for recently diagnosed hairy cell leukemia, developed multiple vesicles over his legs 12 hours after intravenous administration of iopamidol, a nonionic contrast media used for computed tomography (CT) scan. Three days before the onset of lesions, he had undergone his eighth session in a series of diode laser treatments for hair removal, which he tolerated well, showing no immediate injury. The patient denied taking any medication, applying any topical product, or exposing his skin to the sun. Physical examination showed multiple erythematous, vesicular, well-defined, monomorphic plaques all over the legs and thighs. The lesions appeared only on the laser application areas, with healthy skin around (Figure).

Skin biopsies revealed a moderate, polymorphous inflammatory infiltrate of lymphocytes, histiocytes, numerous eosinophils, and some neutrophils, with a superficial and deep perivascular and interstitial distribution. The epidermis showed spongiosis and a slight inflammatory exocytosis.

Oral and topical corticosteroid therapy achieved complete resolution of the lesions without pigmentation or scarring.

Discussion | Severe adverse events of laser treatment include hyperpigmentation and hypopigmentation, crusting, blistering, and scarring. The formation of vesicles after laser treatment is a byproduct of thermal epidermal damage. Epidermal necrosis is expected to be present in the histologic findings of the laser burn.

Histopathologic features of our case are similar to those observed in drug eruptions. Spongiosis and a dermal inflammatory infiltration composed mainly of lymphocytes with a variable number of eosinophils are present in the skin biopsies of cutaneous reactions to iodinated contrast media. In our patient, the distribution of lesions exclusively on laser application areas suggests that the damage caused by the laser was a decisive factor in the onset of drug reaction to the iopamidol used for CT scan.

The pathogenic mechanism of the recall phenomenon is unknown. The onset of the symptoms of recall usually occurs within days to a few weeks after exposure to the precipitating drug, frequently after the first dose, and sometimes during or immediately after intravenous administration.

The marked clinical and histologic differences between the cases induced by different drugs suggest that they are caused by different mechanisms. Any previous insult to the skin would result in increased susceptibility of the local area to the toxic effects of subsequent drug treatments, but probably mechanisms other than a direct toxic effect must be also involved. Some cases may be merely drug reactions confined to areas of previous damage. Although in our case there was no clinically apparent damage, the effect of the previous laser treatment could produce localized edema and vascular changes with increased tissue delivery of drug.

Recall phenomenon has not been associated with laser treatment for hair removal. There is a report of docetaxel-induced recall dermatitis on previous Nd:YAG laser treatment sites.

In conclusion, the temporal relationship between contrast media administration and the appearance of the cutaneous lesions and distribution exclusively on laser treatment sites suggest that this case would correspond to recall phenomenon.