



Primary cutaneous anaplastic large-cell lymphoma: Complete remission for 13 years after denileukin diftitox

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INTRODUCTION

Denileukin diftitox (DD) is a recombinant fusion protein that consists of the interleukin-2 molecule conjugated to the catalytic domain of diphtheria toxin. It targets cells expressing the high-affinity interleukin-2 receptor, such as activated T lymphocytes in cutaneous T-cell lymphoma (CTCL). After binding to the interleukin-2 receptor, DD undergoes endocytosis followed by release of diphtheria toxin, which inhibits protein synthesis and induces subsequent cell apoptosis.

DD was approved by the US Food and Drug Administration in 1999 for the treatment of persistent or recurrent CTCL. However, the pivotal trial leading to the drug's approval only included patients with mycosis fungoides or Sézary syndrome.¹ Although its clinical activity in other forms of CTCL remains unclear, DD may be useful for primary cutaneous anaplastic large-cell lymphoma (pcALCL). We report the case of a patient with recurrent pcALCL who has maintained complete remission (CR) for 13 years after treatment with DD.

CASE REPORT

A 56-year-old white woman presented to MD Anderson Cancer Center in April 2003 with a history of pcALCL. She originally received the diagnosis in November 2002 after papules developed on her right elbow that had enlarged into tumors over several months. Histopathology results were consistent with

Abbreviations used:

CLS:	capillary leak syndrome
CR:	complete remission
CTCL:	cutaneous T-cell lymphoma
DD:	denileukin diftitox
pcALCL:	primary cutaneous anaplastic large-cell lymphoma
Treg:	T-regulatory cell

those of pcALCL. The lesions resolved completely after localized radiation therapy in February 2003. However, several new lesions developed on her abdomen, and she was referred to MD Anderson for further management.

Six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone led to a partial response before progression in October 2003. Physical examination found a 3- × 3-cm tumor on the right lower abdomen (Fig 1, A), 13 papules on her right leg, 3 papules on the dorsal right foot, and a 2- × 1-cm tumor on the instep of the right foot (Fig 1, B). No palpable lymphadenopathy was detected. Positron emission tomography/computed tomography showed no evidence of systemic involvement, and peripheral blood flow cytometry was negative.

Histopathologic examination of the abdominal tumor found a dense, atypical, monomorphous large-cell lymphoid proliferation extending deeply

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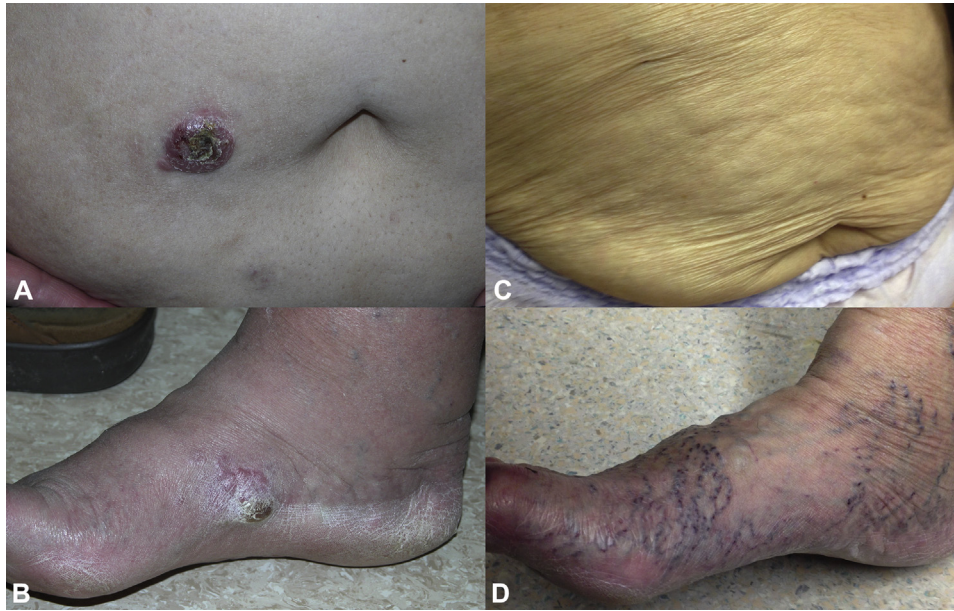


Fig 1. **A**, A 3- × 3-cm pcALCL tumor on the right lower abdomen and **B**, a 2- × 1-cm tumor on the instep of the right foot. **C** and **D**, Ongoing complete resolution of the tumors 13 years after administration of denileukin diftitox.

into the subcutaneous fat, morphologically consistent with pcALCL (Fig 2, A and B). Immunohistochemical studies showed the tissue was negative for anaplastic lymphoma kinase but positive for CD4 and CD30 (Fig 2, C). Some tumor cells showed weak positivity for CD2, CD3, and CD5, and immunostaining for CD8, CD20, PAX-5, and GATA-3 was negative. The tumor cells also exhibited approximately 20% CD25 positivity (Fig 2, D). There were also 46 CD25⁺ FOXP3⁺ cells. Monoclonal T-cell receptor γ -chain gene rearrangements were detected via polymerase chain reaction. Epstein-Barr encoding region in situ hybridization results were negative.

Given the recurrence of lesions and high tumor CD25⁺ expression,² she agreed to treatment with DD. She was patient 1 in a pilot study of an alternate dosing regimen of DD for primary cutaneous peripheral T-cell lymphoma.³ She received one 5-day course of intravenous DD at 18 μ g/kg/d followed by 1 dose per week for 24 weeks. She was prophylactically administered intravenous prednisone, 10 mg, and diphenhydramine, 25 mg, before each infusion to prevent an infusion reaction and 500 mL of normal saline after each infusion to prevent capillary leak syndrome (CLS). In all, she received a total of 29 doses over a 6-month period from December 2003 to June 2004.

Adverse events during treatment were grade 1 nausea, elevated liver enzymes, and CLS. Her nausea resolved with ondansetron, 8 mg. Alanine aminotransferase and aspartate aminotransferase levels

increased from 15 and 16 IU/L at the start of therapy to 129 and 121 IU/L, respectively, and lactate dehydrogenase level increased from 415 to 693 IU/L. She also experienced CLS on cycle 1, dose 5, exhibiting a blood pressure of 95/60 mm Hg, a decrease in albumin level from 3.4 to 3.0 g/dL, and trace pitting edema of the lower legs. Her CLS was successfully managed by discontinuing furosemide, 10 mg, which she had been taking daily for hypertension, for the duration of treatment.

Her pcALCL lesions completely resolved by week 8 (Fig 1, C and D), and a complete pathologic response was confirmed at week 20. Remarkably, she has remained in CR for more than 13 years, as of her last follow-up in January 2017. However, in April 2012, she had stage II (T2N0M0) infiltrating tubular-lobular carcinoma of the right breast, successfully treated with lumpectomy, adjuvant radiation therapy, and maintenance hormonal therapy. She otherwise remains in good health, and her last positron emission tomography/computed tomography scan in February 2013 was unremarkable.

DISCUSSION

Our report describes the longest reported CR of pcALCL, or any form of CTCL, with DD. Previously, excluding our case, the longest CR of pcALCL after treatment with DD was 8 months.⁴ DD may induce long-term remission by inhibiting CD25⁺ T-regulatory cells (Tregs).^{5,6} By depleting Tregs, DD eliminates suppression of CD8⁺ T cells, which are thought

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