

Aggressive primary cutaneous anaplastic large cell lymphoma with massive bilateral upper limb involvement at relapse



Christopher N. Nguyen, BA,^a Swaminathan P. Iyer, MD,^b Roberto N. Miranda, MD,^c Carlos A. Torres-Cabala, MD,^{d,e} Jonathan L. Curry, MD,^d Penny Fang, MD,^f Valencia D. Thomas, MD,^e and Auris O. Huen, MD^c
Houston, Texas

Key words: ALCL; C-ALCL; CD30⁺ LPD; cutaneous lymphoma; CTCL.

INTRODUCTION

Primary cutaneous CD30⁺ lymphoproliferative disorders (LPDs) are the second-most common group of cutaneous T-cell lymphomas after mycosis fungoides and make up about 30% of all cutaneous T-cell lymphoma cases.¹ CD30⁺ LPD of the skin includes lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma (ALCL). Lymphomatoid papulosis and C-ALCL appear histologically similar but can be differentiated clinically. Cutaneous ALCL commonly presents as solitary or grouped nodules, tumors, or plaques that persist or progress if left untreated.² Most cases follow an indolent course and have a favorable prognosis.¹ Cutaneous ALCL frequently relapses to the skin, but 13% of relapsed cases present extracutaneously, usually involving lymph nodes.³ We report a unique case of recurrent cutaneous ALCL that symmetrically infiltrated skeletal muscles of both upper limbs.

CASE DESCRIPTION

A 64-year-old man with no pertinent past medical history presented with a 6-month history of asymptomatic lesions on his upper extremities that were biopsied and diagnosed as CD30⁺ LPD. On physical examination, he exhibited a tumor on the right elbow (2.5 cm × 2 cm) and multiple erythematous papules on the left knee with body surface area involvement of 0.45% (Fig 1). Complete blood count, chemistries, and liver function tests were within normal limits. Flow cytometry of peripheral blood

Abbreviations used:

ALCL:	anaplastic large cell lymphoma
ALK:	anaplastic lymphoma kinase
CHOP:	cyclophosphamide, Adriamycin, vincristine, prednisone
CHP-BV:	cyclophosphamide, doxorubicin, prednisone, and brentuximab vedotin
LPD:	lymphoproliferative disorder

showed no aberrant T-cells, and imaging confirmed the absence of lymphadenopathy and systemic involvement. Repeat skin biopsy showed atypical lymphoid cells in the dermis and subcutaneous tissue expressing CD2 and CD30, but not CD3, CD5, CD7, CD8, CD20, or anaplastic lymphoma kinase (ALK). Based on the clinical course, no clinical support for mycosis fungoides, and the histopathologic and immunohistochemical features, the diagnosis of cutaneous ALCL was favored. The patient received two 300 cGy fractions of radiotherapy on the right elbow, left lateral aspect of the knee, and left medial aspect of the knee (total dose 18 Gy), and the lesions completely cleared.

However, 10 months later, the patient returned with new tumors on the right hand (2 cm × 2 cm) and right elbow (3 cm × 2.5 cm) and plaques on the left knee (body surface area of 0.5%). He also reported swelling of his left hand with numbness and tingling in both hands. Magnetic resonance imaging revealed mild focal myositis and fasciitis at the left elbow. Inflammatory arthropathy and

From the School of Medicine, Baylor College of Medicine^a; and the Department of Lymphoma,^b the Department of Hematopathology,^c the Department of Pathology,^d the Department of Dermatology,^e and the Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center.^f

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Christopher N. Nguyen, BA, 1 Baylor Plaza, Houston, TX 77030. E-mail: christopher.nguyen42@gmail.com.

JAAD Case Reports 2021;17:34-7.

2352-5126

© 2021 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jdc.2021.09.005>



Fig 1. Initial presentation of patient's primary cutaneous anaplastic large cell lymphoma. Right elbow with erythematous, shiny tumor (2.5 cm × 2 cm).

myositis workups by the rheumatologist, including c-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and cyclic citrullinated peptide antibodies, were negative. Aldolase was slightly elevated at 9.7 Sibley-Lehninger units/dL (normal, 3-8.2 Sibley-Lehninger units/dL). The neurologist ruled out carpal tunnel syndrome and attributed the patient's neuropathic symptoms to nerve impingement from swelling. Positron emission tomography/computed tomography revealed diffuse myositis and subcutaneous and cutaneous lesions of bilateral upper extremities; there was no lymphadenopathy or visceral involvement (Fig 2, A). An excisional biopsy of the left biceps showed a diffuse infiltrate of atypical, large lymphoid cells with irregular nuclear contours and cytoplasmic reactivity for CD4, CD30, and p63. The neoplastic cells were negative for CD3, CD7, CD8, CD20, and ALK (Fig 3). Fluorescence in situ hybridization studies demonstrated *DUSP22* gene rearrangement. The patient's swelling and left arm pain were relieved with a short course of prednisone. The case was discussed at a multidisciplinary cutaneous lymphoma conference and determined to be cutaneous ALCL with extracutaneous involvement of the muscle. The patient is currently undergoing treatment with cyclophosphamide, doxorubicin, prednisone, and brentuximab vedotin (CHP-BV). At his 2-month follow-up, his skin lesions resolved, and he had no arm swelling or neuropathic symptoms. Repeat positron emission tomography/computed tomography

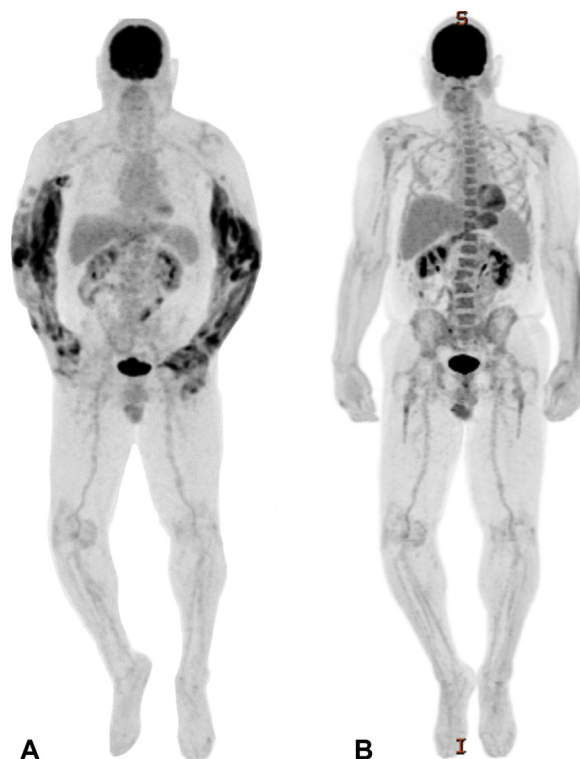


Fig 2. Positron emission tomography/computed tomography of primary cutaneous anaplastic large cell lymphoma. **A**, Prechemotherapy image depicting extensive nodular and curvilinear activity involving cutaneous, subcutaneous, and muscle of bilateral upper extremities. **B**, Postchemotherapy image depicting clearance of lesions and complete remission.

showed complete remission with clearance of all lesions of the bilateral upper extremities (Fig 2, B).

DISCUSSION

Cutaneous ALCL infiltration into the muscle is rare, with only 1 other report found in the literature. Barete et al⁴ reported 2 cases of cutaneous ALCL infiltrating the muscle of a unilateral lower limb, both in immunocompromised patients. Our case differs in that the patient was immunocompetent and experienced bilateral upper limb muscle involvement; a review of the literature did not reveal a similar case.

Cutaneous ALCL generally carries an excellent prognosis, with a 5-year survival rate between 76% and 96% and a 10-year disease-specific survival rate of 85%.^{2,3} Age older than 60 years, involvement of the leg, extensive limb disease, and extracutaneous disease have all been implicated in a worse prognosis.⁵ Of note, by these standards, both patients reported by Barete et al⁴ had an extremely aggressive disease, with both patients dying within 30 months of their initial diagnoses.

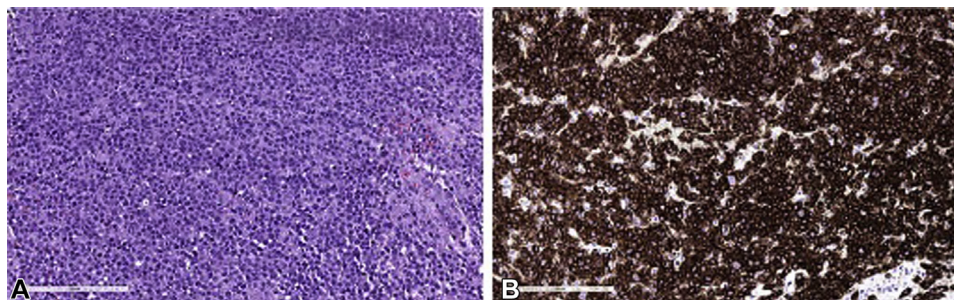


Fig 3. Primary cutaneous anaplastic large cell lymphoma, biopsy of the left bicep. **A**, Diffuse proliferation of atypical, large lymphoid cells replacing skeletal muscle. **B**, The neoplastic cells are diffusely and strongly positive for CD30. (**A**, Hematoxylin and eosin stain and **B**, immunohistochemical stain, anti-CD30; original magnifications: **A**, and **B**, $\times 200$.)

The differential diagnosis of cutaneous ALCL is systemic ALCL—more specifically, ALK-negative ALCL—with secondary cutaneous involvement, as prognosis and treatment vary greatly between these diseases. Systemic ALCL, as its name implies, exhibits systemic, nodal, and extranodal disease. Systemic ALCL positive for ALK has a 5-year overall survival rate of approximately 85% to 90%. In contrast, systemic ALCL negative for ALK exhibits an overall worse prognosis, with a 5-year overall survival of 55%—except the subset of cases that have *DUSP22* rearrangement, which carry an outcome similar to ALK⁺ systemic ALCL.⁶ ALK⁻ systemic ALCL and cutaneous ALCL may both harbor *DUSP22* rearrangement in approximately 30% of the cases. In contrast with cutaneous ALCL, systemic ALCL is generally treated with multiagent chemotherapy.⁷ The patient we describe had no findings of nodal or visceral involvement on presentation, supporting a diagnosis of cutaneous ALCL over ALK⁻ systemic ALCL.^{2,8}

Low-risk patients with cutaneous ALCL are usually treated with skin-directed treatments such as surgical excision or radiation, like our patient. There are multiple systemic therapeutic options for recurrences or widespread disease, such as methotrexate, bexarotene, and BV. Multiagent chemotherapy, most commonly cyclophosphamide, Adriamycin, vincristine, prednisone (CHOP), has not been shown to be better than other treatment protocols, with relapses in 62% of patients; indeed, both Barete et al⁴ patients failed CHOP. Because of this, multiagent chemotherapy is only recommended in cutaneous ALCL for extracutaneous disease or when multiple single-agent systemic therapies have failed.² Systemic ALCL with >10% of cells expressing CD30 can be treated initially with CHP-BV, which has shown improved survival over CHOP in these patients.⁹ For this reason and because our patient's cutaneous ALCL relapsed with features of systemic ALCL, the

patient was treated with CHP-BV and achieved complete remission.

In summary, we report a unique case of bilateral cutaneous ALCL with extensive and symmetrical muscular involvement that may represent the aggressive end of the spectrum of cutaneous ALCL and borderline with ALK⁻ systemic ALCL. Given the multifocal and recurring presentation of cutaneous ALCL confined to the skin, subcutaneous tissue, and skeletal muscle without visceral or nodal involvement, the patient was managed following the guidelines for systemic ALCL.

Conflicts of interest

None disclosed.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785. <https://doi.org/10.1182/blood-2004-09-3502>
2. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood*. 2011;118(15):4024-4035. <https://doi.org/10.1182/blood-2011-05-351346>
3. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH. CD30+ cutaneous lymphoproliferative disorders: the Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol*. 2003; 49(6):1049-1058. [https://doi.org/10.1016/s0190-9622\(03\)02484-8](https://doi.org/10.1016/s0190-9622(03)02484-8)
4. Barete S, Francés C, Charlotte F, Barrou B, Leblond V, Dereure O. Fatal outcome of deep-penetrating lower limb primary cutaneous anaplastic large cell lymphomas in two immunocompromised patients. *Acta Derm Venereol*. 2009;89(6):627-630. <https://doi.org/10.2340/00015555-0682>
5. Brown RA, Fernandez-Pol S, Kim J. Primary cutaneous anaplastic large cell lymphoma. *J Cutan Pathol*. 2017;44(6):570-577. <https://doi.org/10.1111/cup.12937>
6. Shustov A, Soma L. Anaplastic large cell lymphoma: contemporary concepts and optimal management. *Cancer Treat Res*. 2019; 176:127-144. https://doi.org/10.1007/978-3-319-99716-2_6
7. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically

- different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008; 111(12):5496-5504. <https://doi.org/10.1182/blood-2008-01-134270>
8. Lee WJ, Moon IJ, Lee SH, et al. Cutaneous anaplastic large-cell lymphoma (ALCL): a comparative clinical feature and survival outcome analysis of 52 cases according to primary tumor site. *J Am Acad Dermatol*. 2016;74(6):1135-1143. <https://doi.org/10.1016/j.jaad.2015.12.053>
 9. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECH-ELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240. [https://doi.org/10.1016/S0140-6736\(18\)32984-2](https://doi.org/10.1016/S0140-6736(18)32984-2). Published correction appears in *Lancet*. 2019; 393(10168):228.