

An unusual case of cytotoxic peripheral T-cell lymphoma

Casey Wang, MD,^a Nicole Reusser, BA,^{a,d} Megan Shelton, BS,^{a,d} Jace Reed, BS,^c Hung Doan, MD, PhD,^a Carlos Antonio Torres-Cabala, MD,^b Bouthaina Dabaja, MD,^c and Madeleine Duvic, MD^a
Houston and Lubbock, Texas

Key words: α/β T-cell lymphoma; CD56; CD4/CD8 double negative; cutaneous T-cell lymphoma; drug-induced; hydroxychloroquine.

INTRODUCTION

Cytotoxic cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of lymphoproliferative disorders characterized by localization of atypical T cells in the skin that often express CD56 and cytotoxic granules. CTCLs exhibit a wide range of clinical and histopathologic features but tend to be aggressive.¹ Often diagnosis relies heavily on immunohistochemistry. We report a case of cytotoxic CTCL with a unique immunophenotype.

CASE REPORT

A 69-year-old white man had annular plaques on sun-exposed areas of his body. Two lesional biopsies found a lymphocytic infiltrate lacking atypia and monoclonality. Diffuse dermal mucin deposition was observed, consistent with tumid lupus. The patient was treated with topical fluocinonide cream and hydroxychloroquine, 400 mg daily, later increased to 600 mg, with significant improvement. Three months later skin lesions of a different morphology developed: nodules on his upper arms and thighs that enlarged and involuted spontaneously. Lesional biopsies of the right arm and right leg found an atypical population of CD3⁺, CD56⁺, and CD4/CD8 double negative (DN) lymphocytes of medium to large size, consistent with CTCL. Hydroxychloroquine was discontinued, and the patient's nodules resolved.

When the patient presented to us, he had a 1-cm ill-defined indurated nodule on his back, an arcuate lesion on his upper abdomen, and several erythematous patches in sun-exposed areas. A

Abbreviations used:

CD4/CD8 DN:	CD4/CD8 double negative
CTCL:	cutaneous T-cell lymphoma
EBER:	Ebstein-Barr virus-encoded small RNAs
NK:	natural killer
PCGD-TCL:	primary cutaneous gamma-delta T-cell lymphoma
PET/CT:	positron emission tomography/computed tomography
PTCL:	peripheral T-cell lymphoma
SPCTL:	subcutaneous panniculitic cutaneous T-cell lymphoma
TCR:	T-cell receptor

biopsy of the nodule found a predominantly CD3⁺ infiltrate with a normal CD4:CD8 ratio, preserved CD7 expression, and negative CD30 and CD56 expression. There was a mild increase in dermal mucin, consistent with the original diagnosis of tumid lupus. A repeat biopsy 2 weeks later showed only perifollicular granulomatous inflammation. Bone marrow biopsy, peripheral blood flow cytometry, and positron emission tomography/computed tomography (PET/CT) scan were within normal limits. At follow-up 6 months later, the patient remained free of all lesions suggestive of lymphoma.

Two years later, the patient returned with new violaceous annular plaques on the left popliteal fossa, right forearm, and the left thigh (Fig 1, A). He was treated unsuccessfully for 2 months with 0.05% fluocinonide cream. A biopsy of the left popliteal fossa found an atypical dermal lymphocytic infiltrate with focal epidermotropism. The cells were

From the Departments of Dermatology,^a Pathology,^b and Radiation Oncology,^c The University of Texas MD Anderson Cancer Center; The University of Texas Health Science Center at Houston Medical School^d; and Texas Tech University Medical School.^e

Funding sources: None.

Conflicts of interest: None declared.

Correspondence to: Casey Wang, MD, Department of Dermatology, The University of Texas MD Anderson Cancer

Center, Pickens Tower, FCT11.6097, 1515 Holcombe Boulevard, Houston, TX 77030. E-mail: cwang4@mdanderson.org.

JAAD Case Reports 2015;1:257-60.

2352-5126

© 2015 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/>).

<http://dx.doi.org/10.1016/j.jidcr.2015.04.016>



Fig 1. Recurrent cutaneous T-cell lymphoma. **A**, Indurated violaceous plaques with arcuate morphology. **B**, Complete response to radiation.

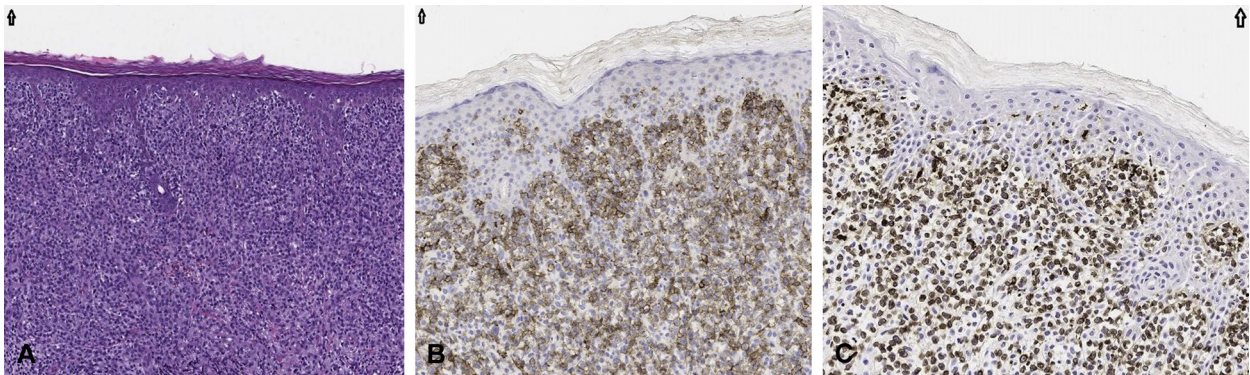


Fig 2. **A**, Histopathologic findings. A dense infiltrate of atypical lymphocytes in the dermis and with focal epidermotropism. **B**, The atypical cells are diffusely positive for CD56. **C**, The atypical infiltrate expresses β F1. (**A**, Hematoxylin-eosin stain; original magnification: $\times 4$; **B** and **C**, Immunohistochemistry; original magnification: $\times 10$.)

$CD3^+$, $CD56^+$, $CD30^-$, and $CD4/CD8$ DN by immunohistochemistry (Fig 2, A-C). TIA1 and granzyme B were positive, and Epstein-Barr virus–encoded small RNAs (EBER) by in situ hybridization were negative. T-cell receptor (TCR) gene rearrangement studies showed β F1 $^+$ and $TCR\gamma^-$. PET/CT and peripheral blood flow cytometry were again unremarkable. The lesions responded to 8 Gy of local electron beam radiation (Fig 1, B). Five months later, the patient had new lesions on his forearms and left thigh. The patient was treated again with local electron beam, with near-complete response to therapy.

DISCUSSION

CTCLs have a wide spectrum of clinical presentations, making lesional biopsy tantamount to diagnosis. Classification of CTCLs follows World Health Organization (WHO)—European Organization for Research and Treatment of Cancer (EORTC) guidelines using clinical, histologic, immunophenotypic, and genetic features.² However, diagnoses are often made based on histopathology alone.

We report an unusual case of CTCL with an unusual $CD3^+$ cytotoxic immunophenotype that is not easily classified under the current WHO-EORTC

Table I. Differential diagnosis for cytotoxic lymphomas

	Our patient	Extranodal NK/TCL	SPCTL	PCGDTCL	Anaplastic large cell lymphoma	CD8 ⁺ aggressive epidermotropic CTCL
Behavior	Indolent	Aggressive	Indolent	Aggressive	Indolent	Aggressive
Immunostaining	CD3 ⁺	CD3 ⁻	CD3 ⁺	CD2 ⁺	CD3 ⁺	CD3 ⁺
	CD4 ⁻	CD4 ⁻	CD4 ⁻	CD3 ⁺	CD4 ⁺	CD4 ⁻
	CD8 ⁻	CD8 ^{-/+}	CD4 ⁻	CD4 ⁻	CD8 ^{-/+}	CD8 ⁺
	CD56 ⁺	CD56 ⁺ (strong)	CD8 ⁺	CD8 ^{-/+}	CD56 ^{-/+}	
			CD56 ^{-/+}	CD56 ^{-/+}	CD30 ⁺	
				CD30 ^{-/+}		
	CD45RO ⁺	CD45RO ⁺				CD45RO ⁻
	CD45RA ⁻	CD45RA ⁻	CD45RO ⁺			CD45RA ⁺
	Perforin ⁺	Perforin ⁺		Perforin ⁺		
	Granzyme B ⁺	Granzyme B ⁺		Granzyme B ⁺	Granzyme B ⁺	
	TIA1 ⁺	TIA1 ⁺	Granzyme B ⁺	TIA1 ⁺	TIA1 ⁺	TIA1 ⁺
			TIA1 ⁺			
TCR gene	TCR γ/δ ⁻	No TCR rearrangement	TCR γ/δ ⁻	TCR γ/δ ⁺	Variable	Variable
	TCR β F1 ⁺		TCR β F1 ⁺	TCR β F1 ⁻		
EBV status	EBER ⁻	EBER ⁺	EBER ⁻	EBER ⁻	EBER ^{-/+}	EBER ⁻
Histology	Atypical dermal infiltrate of medium to large cells with epidermotropism	Dense diffuse infiltrates; small to large cells with pleomorphic nuclei and pale cytoplasm	Variably sized pleomorphic infiltrating fat lobules and resemble lobular panniculitis; frequently with fat necrosis & foamy histiocytes	Epidermotropic (pagetoid) vs dermal (diffuse or nodular) \pm subcutaneous component. Infiltrate composed of medium to large cells w/irregular chromatin-dense or vesicular nuclei, angioinvasion, & necrosis common	Nodular cohesive infiltrates of large pleomorphic, anaplastic, or immunoblastic tumor cells (>75% must be CD30 ⁺)	Bandlike epidermotropic infiltrate of small-medium or medium-large lymphocytes w/pleomorphic chromatin-dense nuclei. Numerous apoptotic necrotic keratinocytes and spongiosis
	Clinical presentation	Localized deep red annular plaques	Subcutaneous plaques or nodules	Generalized often necrotic or ulcerated papules, plaques, or nodules; mucosal and organic involvement common	Solitary nodules or tumors	Widespread plaques and nodules, often with hemorrhage and ulceration

Data from Willemze et al.²⁻⁴ and Santucci et al.⁶

guidelines.^{2,3} Several other cytotoxic CTCL entities were considered in the differential diagnosis, including subcutaneous panniculitic cutaneous T-cell lymphoma (SPTCL), primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL), extranodal natural killer (NK)/TCL, cutaneous anaplastic large cell lymphoma, and CD8⁺ aggressive epidermotropic CTCL (Table I). Although our patient's CTCL had a CD4/CD8 DN, CD56⁺ phenotype, and cytotoxic molecule expression (TIA1, perforin, granzyme B), features suggestive of PCGD-TCL and extranodal NK/T-cell lymphoma, the expression of the β F1 TCR precludes classification as a PCGD-TCL. β F1 positivity is seen in SPTCLs, which can also express CD56 and cytotoxic molecules and typically exhibits an indolent course, but the patient's lack of subcutaneous involvement is inconsistent with such.^{2,4} The negative EBER challenged the diagnosis of extranodal NK/T-cell lymphoma.^{2,3} Primary cutaneous anaplastic large cell lymphoma is rarely CD56⁺, but its diagnosis requires more than 75% CD30 positivity, a feature this case consistently lacked.² It is important to note that the EBER staining method detects Epstein-Barr virus RNA by in situ hybridization. False-negative readings result from RNA degradation in the tissue and can be prevented with controls such as the polyT probe.⁵ We routinely use positive and negative controls for our in situ hybridization for EBER.

Only rarely have CD3⁺, CD4/CD8 DN CTCLs been reported and most possess the γ/δ TCR unlike our patient's variant, which is β F1⁺/ γ ⁻1, indicating an α/β phenotype.^{6,7} In a study of 48 cases of cytotoxic CTCLs, 5 cases of CD4/CD8 DN peripheral T-cell lymphoma (PTCL) unspecified were reported. Two of these cases were β F1⁺. It is unknown whether CD56 was positive in these cases. It was noted that a subset of unspecified PTCLs are indolent.⁸ There is an uncommon variant of epidermotropic mycosis fungoides that is CD4/CD8 DN and β F1⁺/ γ ⁻ and portends an indolent course.⁶ Otherwise, most CD4/CD8 DN lymphomas exhibit an aggressive course that is often refractory to treatment.⁷ CD56 is a nonspecific marker of NK cells

and is not only seen in NK lymphomas but also in PCGD-TCLs, another aggressive disease.^{2,3} The concomitant expression of CD56 and α/β TCR with cytotoxic granule proteins has not been previously described.

The patient's initial diagnosis with tumid lupus and lymphomatous lesions that spontaneously resolved is also unusual. Given that early-stage CTCL can mimic benign conditions, the patient's presentations likely represent one clinical entity. Under WHO-EORTC guidelines, this patient's disease is best classified as a peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).^{2,3} Because PTCL-NOS can be systemic, complete lymphoma staging was done to screen for blood, lymph node, and bone marrow involvement using peripheral blood flow cytometry, PET-CT, and bone marrow biopsy. There is no standard treatment for PTCL-NOS. The patient was treated with skin-directed electron beam therapy because he has stage I disease limited to the skin.

REFERENCES

- Guitart J, Weisenburger DD, Subtil A, et al. Cutaneous gamma-delta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. *Am J Surg Pathol*. 2012;36(11):1656-1665.
- Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785.
- Willemze R, Meijer CJ. Classification of cutaneous T-cell lymphoma: from Alibert to WHO-EORTC. *J Cutan Pathol*. 2006;33:18-26.
- Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood*. 2008;111:838-845.
- Weiss LM, Chen YY. EBER in situ hybridization for Epstein-Barr virus. *Methods Mol Biol*. 2013;999:223-230.
- Hodak E, David M, Maron L, Aviram A, Kaganovsky E, Feinmesser M. CD4/8 double-negative epidermotropic cutaneous T-cell lymphoma: an immunohistochemical variant of mycosis fungoides. *J Am Acad Dermatol*. 2006;55(2):276-284.
- Jones D, Vega F, Sarris AH, Medeiros LJ. CD4/CD8 "double negative" cutaneous T-cell lymphomas share common histologic features and an aggressive clinical course. *Am J Surg Pathol*. 2002;26(2):225-231.
- Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphoma. Report of EORTC cutaneous lymphoma task force workshop. *Cancer*. 2003;97(3):610-627.