A rare case of aggressive cytotoxic T-cell lymphoma in a patient on dupilumab

Renat Ahatov, BSA,[a] Allison J. Good, MD,[b] Michael Joo, MD,[c] Shelby Tipton, MD,[c] Brandon Goodwin, MD,[b,d] and Brent Kelly, MD[b,d]
Galveston, Texas

Key words: cytotoxic T-cell lymphoma; dupilumab; primary cutaneous γδ T-cell lymphoma.

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are a heterogenous group of neoplasms with monoclonal T-cell proliferation involving the skin. Primary cutaneous γδ T-cell lymphoma (PCGD-TCL) is a rare variant of CTCL.[1] PCGD-TCL is aggressive, with a 5-year survival rate of <5%.[2] We present a case of a 62-year-old woman, who received dupilumab therapy, and who presented with a generalized rash with widespread polycyclic erosions and ulcers. A biopsy was consistent with aggressive cytotoxic T-cell lymphoma, and PCGD-TCL was most favored.

CASE REPORT

A 62-year-old woman was hospitalized for a severe rash. The patient reported a history of a rash persisting since she was a teenager with a presumed diagnosis of atopic dermatitis. The rash was described as erythematous, pruritic, and occasionally associated with crust. She saw several dermatologists, and multiple previous biopsies had been non-diagnostic. She was started on dupilumab by a dermatologist about 1.5 years prior to her hospitalization with improvement in the rash only on her lower extremities, but with no overall resolution of her rash. No other systemic agents had been tried previously. One year after starting dupilumab, she noted multiple painful coalescing ulcerations on the abdomen. She was seen by a dermatologist, who recommended supportive wound care, and started cefalexin and levofloxacin for 3 weeks. Despite the use of antibiotics, the ulcers continued to spread gradually, and she presented to the hospital.

Abbreviations used:

CTCL:	cutaneous T-cell lymphoma(s)
PCGD-TCL:	primary cutaneous γδ T-cell lymphoma(s)

Physical examination showed diffuse erosions and ulcerations (Fig 1). Biopsy showed lichenoid and interface dermatitis with pigment incontinence and eosinophils. An additional biopsy was taken, revealing dense lichenoid and vacuolar-interface dermatitis with ulceration and abundant eosinophils; neither showed evidence of CTCL. Direct immunofluorescence, paraneoplastic pemphigus antibody screen, and HIV, rapid plasma reagin, and human T-lymphotropic virus type I/II antibody tests were negative. Based on a working diagnosis of lichenoid drug eruption, treatment with systemic steroids was initiated. Steroid treatment was discontinued after 5 days due to new onset of fever and no improvement in her skin lesions. Another biopsy was taken from the edge of one of the patient's ulcerations. While results were pending, the patient's clinical status deteriorated. She developed fevers and became hemodynamically unstable. Blood cultures grew *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and polymerase chain reaction on DNA extracted from her wounds was positive for herpes simplex virus type 1. Septic shock was suspected. Despite antibiotics, vasopressor support, and intubation, the patient died. The results of the biopsy showed a dense mixed hematolymphoid dermal and subcutaneous infiltrate with perivascular

From the School of Medicine[a]; Department of Dermatology[b]; Department of Internal Medicine[c]; and Department of Dermatopathology, The University of Texas Medical Branch, Galveston.[d]

Funding sources: None.
IRB approval status: Not applicable.

Correspondence to: Allison J. Good, MD, Dermatology Resident, Department of Dermatology, University of Texas Medical Branch at Galveston, 301 University Blvd, 4.111 McCullough Building, Galveston, TX 775550. E-mail: ajgood@utmb.edu.

JAAD Case Reports 2022;24:112-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.04.023

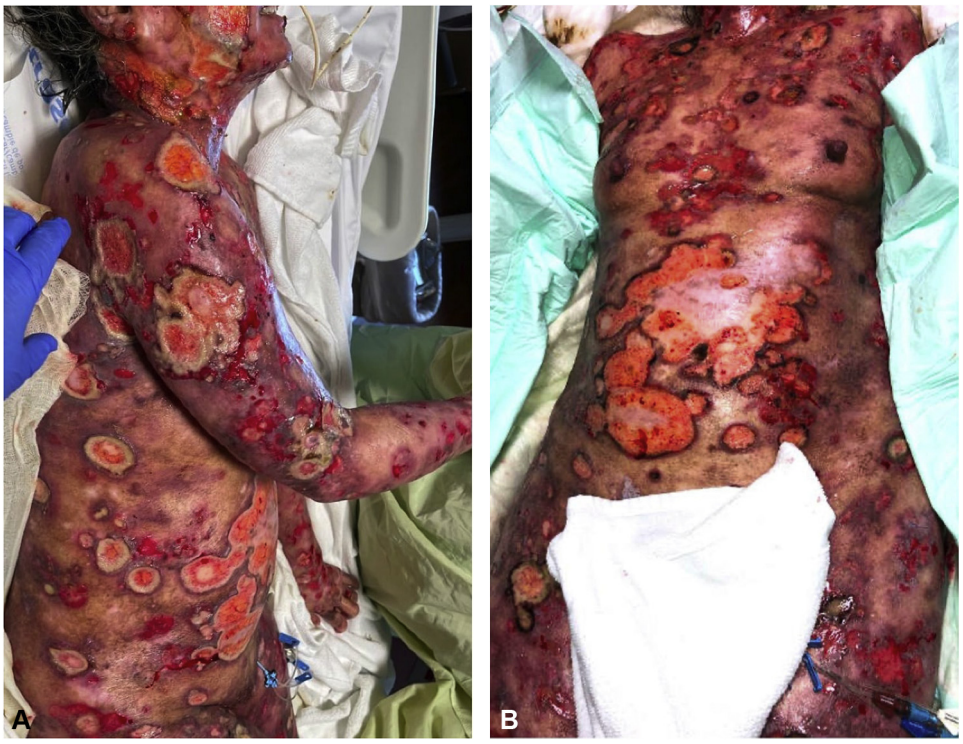

Fig 1. Clinical presentation of PCGD-TCL. Diffuse, polycyclic, well-defined erosions and ulcers with a background of hyperpigmented patches and macules. Shown are the patient's right side (**A**) and trunk/chest (**B**) with the lesions.

medium-to-large atypical CD45+/CD3+/CD4-/CD8-/CD5-/CD7-/CD30-/CD56-/Granzyme-B +/Perforin+/TIA-1- lymphocytes with cerebriform nuclear contour and hyperchromatic nuclei (Fig 2). PCR for T-cell receptor γ gene rearrangement was indeterminate. There was a clonal population of T cells as well as a polyclonal population of T-cell receptor gene rearrangement products. Overall, the clinical presentation, histopathologic features, immunophenotype, and molecular studies were consistent with an aggressive cytotoxic T-cell lymphoma, and PCGD-TCL was the most favored diagnosis.

DISCUSSION

PCGD-TCL is caused by clonal proliferation of $\gamma\delta$ T-cell receptor- and cytotoxic molecule-expressing T cells.[3] It is a rare subtype of CTCL and accounts for 1% of all primary CTCL.[4] The clinical presentation of PCGD-TCL varies but typically exhibits large, indurated plaques or nodules with superimposed ulceration, erosions, and necrosis. Early presentation of PCGD-TCL often involves psoriasis-like erythematous plaques and patches, which later evolve into the ulcerating lesions.[3,4] Histopathologic analysis of PCGD-TCL generally reveals perivascular infiltrates and cytotoxic changes to the dermo-epidermal junction, dermis, and subcutaneous tissues. Epidermotropism is also present. Immunohistochemical analysis shows βF1$^-$, CD3$^+$, CD2$^+$, CD4$^-$, CD5$^-$, CD8$^-$, CD56$^+$.[1] PCGD-TCL is aggressive, with a median survival of 15-31 months.[5] However, there have been cases of successful treatment and remission with radiation therapy followed by chemotherapy.

There have been several recent reports of CTCL exacerbation in the setting of dupilumab use.[6] CTCL may clinically resemble atopic dermatitis, and histopathologic examination does not always readily reveal CTCL. It is currently unknown if dupilumab unmasks underlying CTCL, or if perhaps it triggers conversion to CTCL via an immunomodulatory shift.[6] More research is needed to elucidate a potential relationship between CTCL and dupilumab. We present here a case of aggressive cytotoxic T-cell lymphoma in a patient receiving dupilumab, which adds to the growing literature about worsening CTCL following treatment with dupilumab. It is important to monitor patients diligently after beginning

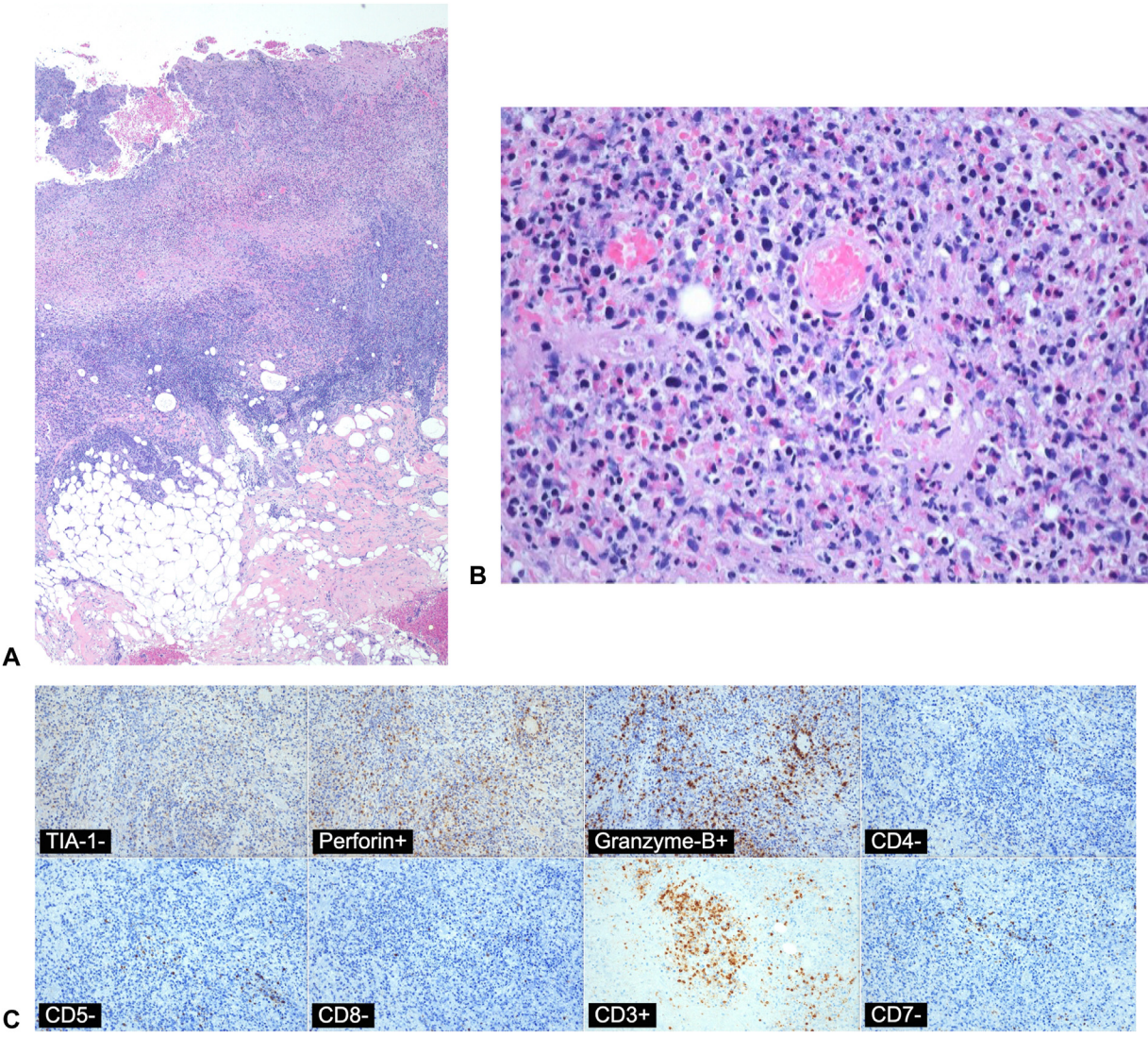

Fig 2. Histopathology and immunofluorescence microscopy. **A,** ×40 micrograph: dense, mixed hematolymphoid dermal and subcutaneous infiltrate with angiodestruction, dermal necrosis, and overlying epidermal ulceration. **B,** ×400 micrograph: perivascular, medium-to-large atypical lymphocytes with cerebriform nuclear contour and hyperchromatic nuclei with notable angiotropism. **C,** Immunoprofile of the atypical lymphocytes (CD56-; not shown).

dupilumab, particularly those who do not respond, and to consider CTCL in the differential diagnosis if the rash progresses or fails to respond as expected.

Conflicts of interest

None disclosed.

REFERENCES

1. Pulitzer M. Cutaneous T-cell lymphoma. *Clin Lab Med*. 2017; 37(3):527-546. https://doi.org/10.1016/j.cll.2017.06.006
2. 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
3. Geller S, Myskowski PL, Pulitzer M. NK/T-cell lymphoma, nasal type, γδ T-cell lymphoma, and CD8-positive epidermotropic T-cell lymphoma-clinical and histopathologic features, differential diagnosis, and treatment. *Semin Cutan Med Surg*. 2018;37(1): 30-38. https://doi.org/10.12788/j.sder.2018.020
4. Geller S, Myskowski PL, Pulitzer M, Horwitz SM, Moskowitz AJ. Cutaneous T-cell lymphoma (CTCL), rare subtypes: five case presentations and review of the literature. *Chin Clin Oncol*. 2019;8(1):5. https://doi.org/10.21037/cco.2018.11.01
5. Damasco F, Akilov OE. Rare cutaneous T-cell lymphomas. *Hematol Oncol Clin North Am*. 2019;33(1):135-148. https://doi.org/10.1016/j.hoc.2018.08.004
6. Russomanno K, Carver DeKlotz CM. Acceleration of cutaneous T-cell lymphoma following dupilumab administration. *JAAD Case Rep*. 2020;8:83-85. https://doi.org/10.1016/j.jdcr.2020.12.010