Peripheral T-cell lymphoma, not otherwise specified, presenting with generalized ulcerated plaques and hypereosinophilia

Aditi Jani, MS,[a] Matthew Innes, MD,[a] Vishnu Reddy, MD,[b] Carlos N. Prieto-Granada, MD,[b] Lauren V. Graham, MD, PhD,[a] and Elizabeth N. Ergen, MD[a]
Birmingham, Alabama

Key words: allergic contact dermatitis; ammonium nitrate; concentric rings; eosinophilic spongiosis; interleukin-5; peripheral T-cell lymphoma.

INTRODUCTION

T-cell lymphomas and leukemias are associated with a variety of dermatologic manifestations including pruritus, erythroderma, papules, patches, plaques, nodules, ulcers, hypopigmentation, alopecia, and slack skin. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), is a non-Hodgkin lymphoma included in the World Health Organization classification of lymphoid neoplasms.[1] The incidence in the United States is 0.4 cases per 100,000 and increasing.[2] PTCL-NOS is a heterogeneous group of lymphomas caused by clonal proliferation of T cells with a mature phenotype that cannot be classified more specifically.[3] Skin is the second most commonly involved site after lymph nodes. Approximately 20% of cases present in the skin, with or without concurrent systemic disease, termed *systemic PTCL-NOS* and *primary cutaneous PTCL-NOS*, respectively. The prognosis is poor.

CASE REPORT

A woman in her 50s with no significant medical history presented with a 6-month history of an itchy rash and gradually enlarging sores of her scalp, trunk, and extremities. She was treated for contact dermatitis with prednisone and topical steroids without resolution. She denied weight loss, night sweats, or fevers. She reported a 25-year history of occupational exposure to ammonium nitrate fertilizer and recounted being detained at airport security because of detection on her skin. Examination revealed the skin findings described in Fig 1 and a pink plaque of the bulbar conjunctiva of the left eye.

Abbreviation used:

PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified

Initial laboratory values, of blood drawn while on prednisone, showed a white blood cell count of 9,700 cells/μL with 17% eosinophils (absolute eosinophil count, 1,649 cells/μL), which increased to 39,000 cells/μL with 56% eosinophils (absolute eosinophil count, 21,840 cells/μL) off of prednisone. Flow cytometry on peripheral blood found no evidence of an aberrant myeloid or lymphoid population, but a clonal T-cell receptor gene rearrangement was detected. Serum lactate dehydrogenase was elevated at 308. A computed tomography scan of the head, neck, chest, abdomen, and pelvis found a 3-cm nodular consolidation in the left lower lobe of the lung (Fig 1). There was no lymphadenopathy or hepatosplenomegaly.

A bone marrow biopsy found hypocellular marrow (20%) with trilineage hematopoiesis and eosinophilia. Flow cytometry of marrow was negative for an aberrant lymphoid or myeloid population. A clonal T-cell receptor gene rearrangement was detected, matching the clone identified in the peripheral blood.

Several skin biopsies over the course of 4 months were reported as eosinophilic spongiosis, with negative direct immunofluorescence. Wound cultures grew abundant *Staphylococcus aureus* and *Stenotrophomonas maltophilia*. Biopsies of a plaque

From the Departments of Dermatology[a] and Pathology,[b] University of Alabama at Birmingham.
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Elizabeth N. Ergen, MD, UAB Department of Dermatology, 500 CEFH, 1720 2nd Ave. S, Birmingham, AL 35294-0009. E-mail: case.elizabeth@gmail.com.

JAAD Case Reports 2018;4:651-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.05.013

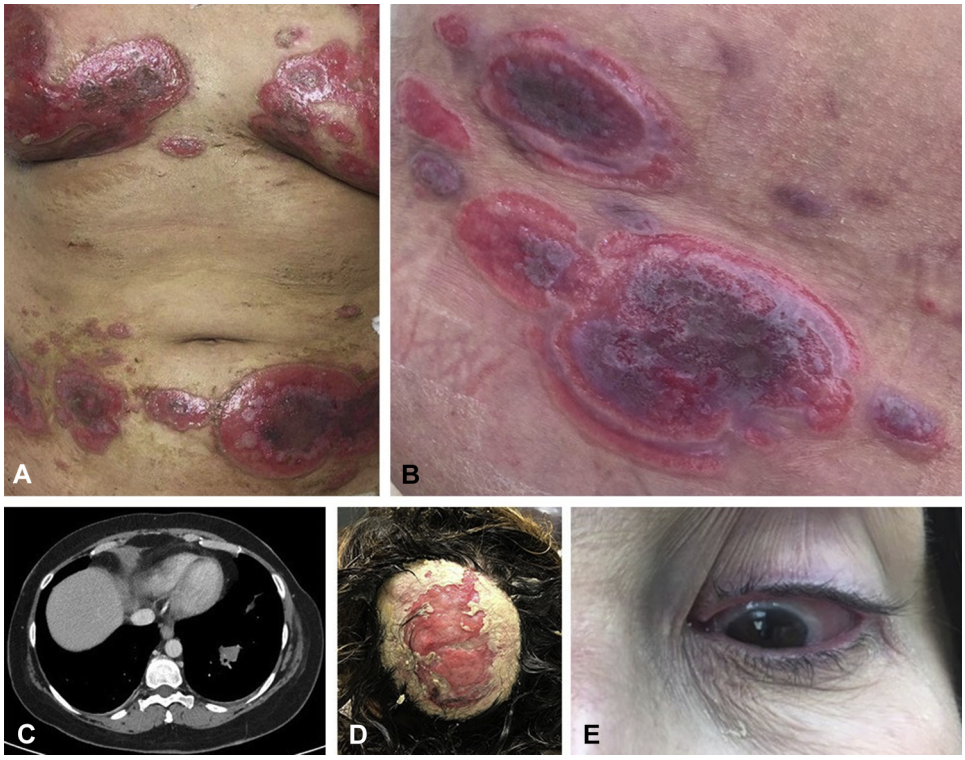

Fig 1. **A**, Annular, ulcerated, erythematous-violaceous plaques ranging in diameter from 1 to 20 cm, predominantly located on the breasts, axillae, low-abdomen, back, groin, and proximal extremities. **B**, Concentric arcs of ulceration noted in many lesions. **C**, A 3-cm nodule in the left, lower lobe of the lung. **D**, A 20-cm ulcerated plaque on the posterior scalp with adherent fibrinopurulent exudate. **E**, Fleshy, pink mass of the left bulbar conjunctiva.

on the trunk and a scalp mass found an atypical T-cell infiltrate described in Fig 2.

Flow cytometry on the scalp mass (Fig 3) found an aberrant T-cell population with the following immunophenotype: $CD2^-$, $CD3^+$, $CD4^-$, $CD5^-$, $CD7^-$, $CD8^-$, $CD16^-$, $CD56^-$, CD10dim, and $\gamma\delta$ T-cell receptor negative. Flow cytometry on a transbronchial lung biopsy found a matching aberrant T-cell population.

An extensive workup for eosinophilia found normal B12, tryptase, IgA, IgE, IgM, and IgG subclasses. Antineutrophil cytoplasmic antibodies were negative. No *FIP1L1-PDGFRA* fusion, *PCM1-JAK2* fusion, *PDGFRB* rearrangement at 5q33.2, *KIT* Asp816Val mutation, or *BCR/ABL* translocation was detected. The patient's karyotype was normal. An infectious workup was negative for antibodies to HIV, human T-lymphotropic virus-1, Strongyloides, and Coccidioides. Histoplasma and Blastomyces antigens were not detected. The serum interleukin-5 level was 24 pg/mL (normal value is 5 pg/mL or less).

PTCL-NOS was diagnosed, and, in coordination with the oncology department, the patient was given 400 mg/m^2 cyclophosphamide, 25 mg/m^2 doxorubicin, and 1 mg vincristine on day 1 and 40 mg/m^2 prednisone on days 1 through 5 (mini-CHOP), followed by skin radiation. She improved, with resolution of her peripheral eosinophilia, decreased pruritus, and regression of some skin lesions. Unfortunately, she died of sepsis within 2 months of her diagnosis.

DISCUSSION

Hypereosinophilia (defined as an absolute eosinophil count greater than 1,500 cells/μL documented on two occasions separated by at least one month and/or histopathology demonstrating tissue hypereosinophilia) manifesting with dermatitis, pruritus, and peripheral eosinophilia initially dominated the clinical picture, leading to a diagnosis of an allergic dermatitis. Hypereosinophilia has multiple possible causes, such as infectious, allergic, neoplastic, or acquired genetic mutations. The hypereosinophilic syndrome is defined as hypereosinophilia and associated tissue damage without an identifiable etiology. In this case, a lymphoma was ultimately identified. Further workup excluded other etiologies. Interleukin-5 was elevated in this case. This cytokine is involved in eosinophil differentiation,

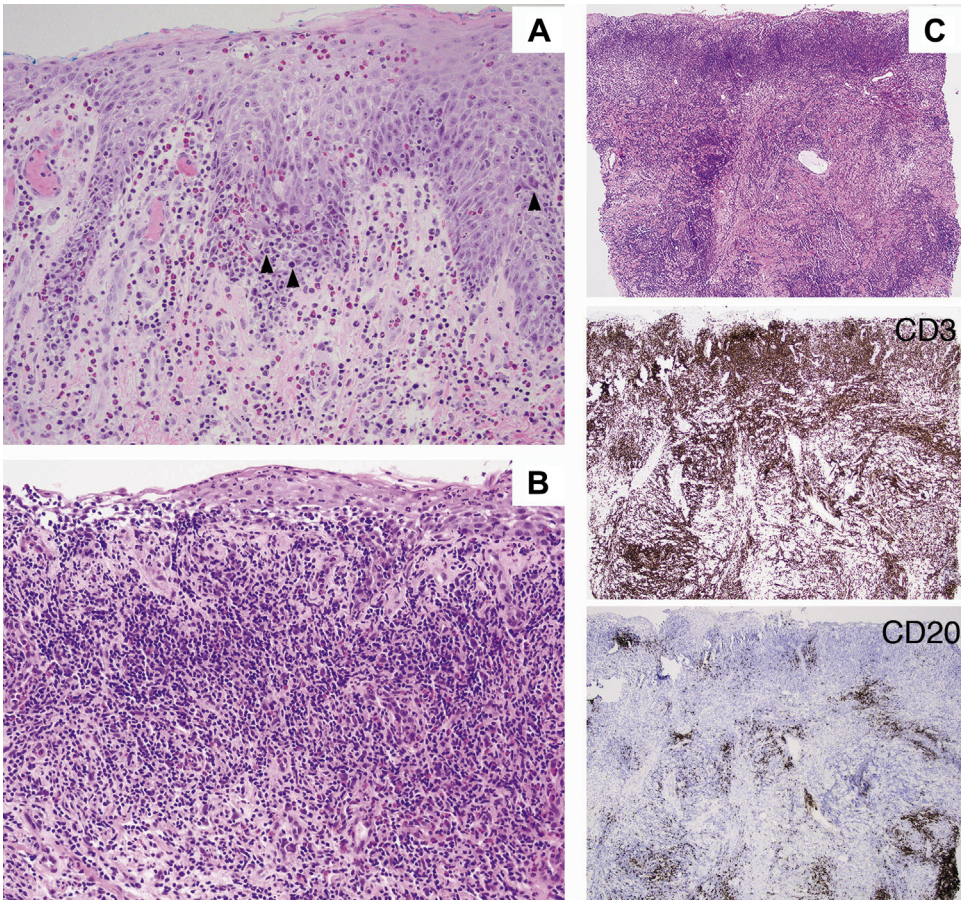

Fig 2. A, Histopathology from the edge of a plaque on the trunk exhibiting eosinophilic spongiosis with scattered hyperchromatic lymphoid cells with convoluted nuclear membranes (*arrowheads*). **B**, View from the center of an ulcerated scalp mass shows an epidermal and superficial dermal lymphoid infiltrate. **C**, Image of the scalp lesion with a dense lymphocytic infiltrate involving the entire thickness of the skin and superficial subcutaneous tissue. **Right-middle**, Cells are atypical, hyperchromatic, and overwhelmingly $CD3^+$. Additional immunohistochemical stains (not shown) showed the atypical cells to be $CD4^-$, $CD5^-$, $CD8^-$, $CD56^-$, $GM3^-$, granzyme b^- and TdT^-. Less than 1% of the total infiltrate was $CD30^+$. Epstein Barr virus in situ hybridization was negative. A βF1 stain was positive, indicating the T-cells had rearranged their α and β T-cell receptor genes. **Right-bottom**, A CD20 stain highlighted only scattered reactive B cells. (Original magnifications: **A** and **B**, ×100; **C**, ×40.)

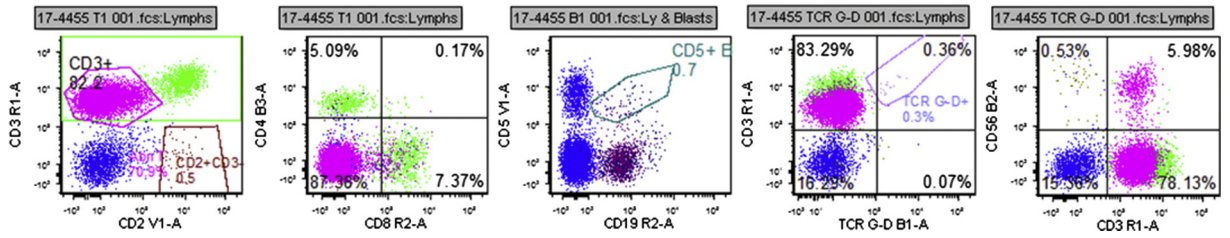

Fig 3. Flow analysis of the scalp mass.

peripheral release, chemotaxis, and survival. The source could have been the malignant T-cell clone[4] or an antitumor response. Hypereosinophilia is reported in some cases of PTCL-NOS.

Ulcerated plaques led to an initial differential diagnosis including autoimmune bullous diseases, neutrophilic dermatoses, and cutaneous lymphomas. Although the skin lesions of PTCL-NOS

are often multifocal and include plaques with ulceration,[5,6] this diagnosis is rarely encountered in dermatology clinics. We are not aware of publication of a case of PTCL-NOS with images of similar skin lesions. The initial histopathology (eosinophilic spongiosis) did not match the clinical differential diagnosis, and it was only after doing additional biopsies that the diagnostic features of PTCL-NOS were apparent. Other investigators have noted that the diagnosis can be challenging because a dense inflammatory infiltrate may surround tumor cells, malignant T cells may have mild cytologic atypia, and PTCL cells lack a pathognomonic T-cell immunophenotype (typically $CD3^+$ and $CD4^+$, but many immunophenotypes occur).[2,7]

The patient's skin ulcers, colonized with pathogenic bacteria, were a factor in the decision to offer dose-reduced chemotherapy in hopes of shortening the duration of neutropenia. Unfortunately, she died of sepsis while recovering from chemotherapy. PTCL-NOS carries a poor prognosis, with 5-year disease-specific survival rate of 16% to 36%.[3,8] Age, performance status, lactate dehydrogenase level, and bone marrow involvement are independent predictors of survival.[9] Treatment with combination chemotherapy, containing an anthracycline, is commonly offered, but this does not appear to give a significant survival advantage.[8] A nuanced understanding of this heterogeneous group of aggressive lymphomas and targeted treatment options are lacking.

A notable feature of this case was the patient's 25-year history of exposure to ammonium nitrate, a fertilizer and explosive, which is a known irritant, predominately of the respiratory tract and eyes. Ammonia exposure has been associated with non-Hodgkin lymphoma in an epidemiologic case-control study.[10]

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
2. Abouyabis AN, Shenoy PJ, Lechowicz MJ, et al. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. *Leuk Lymphoma*. 2008;49:2099-2107.
3. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
4. Matsunaga T, Sato T, Iyama S, et al. [Peripheral T-cell lymphoma presenting with eosinophilia due to interleukin-5 produced by lymphoma cells]. *[Rinsho Ketsueki] Japan J Clin Hematol*. 2006;47:1457-1462.
5. Bekkenk MW, Vermeer MH, Jansen PM, et al. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. *Blood*. 2003;102:2213-2219.
6. Tolkachjov SN, Weenig RH, Comfere NI. Cutaneous peripheral T-cell lymphoma, not otherwise specified: a single-center prognostic analysis. *J Am Acad Dermatol*. 2016;75:992-999.
7. Wallett A, Ibbetson JS, Kearney D, et al. Cutaneous manifestations of peripheral T-cell lymphoma, not otherwise specified: a case series highlighting the diagnostic challenges for this heterogeneous group. *Australas J Dermatol*. 2015;56:197-201.
8. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. *Blood*. 2011;117:3402-3408.
9. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. *Blood*. 2004;103:2474-2479.
10. Fritschi L, Siemiatycki J. Lymphoma, myeloma and occupation: results of a case-control study. *Int J Cancer*. 1996;67:498-503.