JAMA Dermatology Clinicopathological Challenge

Numerous Pink-Purple Papules in a Middle-aged Man

Michael R. Stephens, BA; Paul L. Haun, MD; Robert G. Micheletti, MD

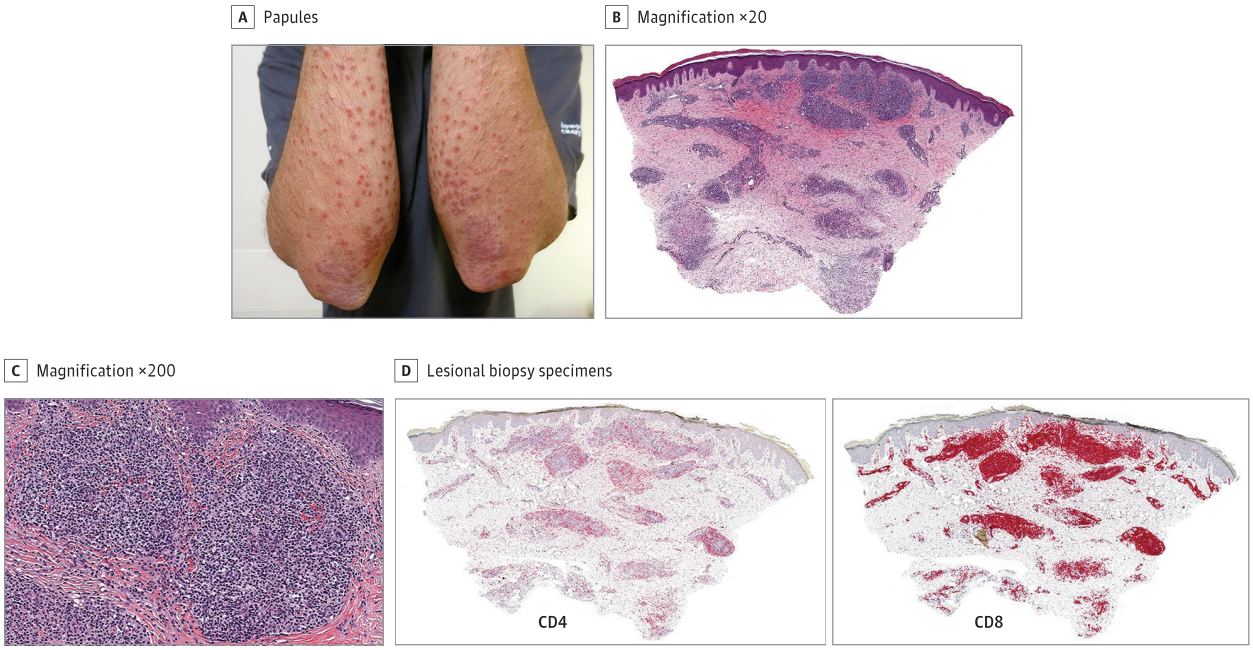

Figure. A, Pink-purple papules on the extensor surface of the arms. B, Biopsy results show a nodular to diffuse lymphohistiocytic infiltrate (hematoxylin-eosin). C, Admixed atypical, irregularly contoured lymphocytes with numerous histiocytes are present. D, Biopsy results show low CD4 signal and robust CD8 signal (magnification ×20).

A man in his 50s was referred to the dermatology clinic with a diagnosis of granuloma annulare made on the basis of prior skin biopsy results. He had been treated by a rheumatologist for polyarticular inflammatory arthritis involving the wrists, metacarpophalangeal joints, and proximal interphalangeal joints, as well as fatigue and dyspnea on exertion. Examination revealed numerous, pink-purple dermal papules on the trunk and extremities, with preference for the extensor surfaces of the arms (Figure, A) and legs. No lymphadenopathy was noted. The patient reported a 5- to 7-kg weight loss without fever or sweats. His pulmonary and joint symptoms were relieved by daily oral prednisone and flared with taper below 10 mg. Other medications prescribed included hydroxychloroquine, 400 mg, daily for 18 months and weekly adalimumab injections for 7 months, without improvement.

Pulmonary function testing revealed mild restrictive disease with decreased forced vital capacity and total lung capacity. Results of a complete blood cell count and metabolic panel; hemoglobin $A1_c$; viral and rheumatologic panels, including HIV blood tests; chest radiograph; high-resolution chest computed tomographic scan; echocardiography; endoscopic studies; hand radiographs; and serum and urine protein electrophoresis were normal or otherwise unremarkable. The results of lesional skin biopsies obtained from multiple involved sites initially revealed nonspecific granulomatous dermatitis before a diagnostic biopsy was performed (Figure, B, C, and D).

WHAT IS YOUR DIAGNOSIS?

A. Cutaneous T-cell lymphoma

B. Granuloma annulare

C. Small-vessel vasculitis

D. Sarcoidosis

Diagnosis

A. Cutaneous T-cell lymphoma

Microscopic Findings

On further histopathological evaluation, lymphocytes present in skin biopsy specimens stained positive for CD3, with an inverted CD8 to CD4 ratio, and were predominantly α/β positive. Many CD8-positive cells displayed hyperchromicity, irregular nuclear contours, and focal perinuclear halos. Most T cells were α/β positive, and few γ/δ-positive cells were present. Staining with CD30 highlighted rare scattered cells, and CD56 results were negative. Flow cytometric analysis of bone-marrow aspirate revealed lymphocytes with an atypical CD3-negative, CD4-negative, CD5-positive, CD8-positive phenotype representing 2% of total cells. Quantitative immunoglobulins testing and Epstein-Barr encoding region in situ hybridization of tissue and bone marrow were performed, and the results were negative. Matching clonal rearrangements were identified through T-cell receptor polymerase chain reaction on 3 skin biopsy specimens and a bone marrow sample. Based on the histopathologic findings, the patient was diagnosed with CD8-positive granulomatous cutaneous T-cell lymphoma (CTCL).

Discussion

Cutaneous T-cell lymphoma encompasses a diverse group of cutaneous neoplasms characterized by clonal T-cell proliferation with heterogenous histological and clinical features.[1] In most cases, the implicated clone is a skin-homing CD4-positive memory T cell; however, rare cases of CD8-positive CTCL have been reported, with variable prognosis ranging from indolent to aggressive.[1-3]

Clinical subtypes in CD8-positive CTCL overlap with those seen in CD4-positive CTCL and include granulomatous variants.[1,2] Granulomas are a well-known feature of nodal lymphomas; however, granulomatous CTCL (GCTCL) is itself a rare entity noted in only 2% of all CTCL cases.[2,4,5] Given its rarity, GCTCL is not yet fully understood or recognized in the World Health Organization classification of cutaneous lymphomas. However, it is considered a separate entity from mycosis fungoides, granulomatous slack skin, and granulomatous mycosis fungoides. Whether granuloma formation represents a specific disease variant or is due to nonspecific reactive inflammation is unclear.[5] Granulomatous CTCL is commonly misdiagnosed as granulomatous dermatitis or similar conditions if lymphocytic atypia is not readily detectable on biopsy results.[3,4,6] In 1 report, a patient with CD8-positive CTCL was initially misdiagnosed with granuloma annulare; it is likely that the present patient was similarly misdiagnosed.[3] The clinical course of GCTCL has not been established. Early reports of improved prognosis have been followed by later reports documenting prognosis similar to that of other CTCL variants.[2,4,6]

Given the rarity of both CD8-positive CTCL and GCTCL, only 9 other cases of CD8-positive GCTCL have been documented in the literature. Most patients were noted to have erythematous papules and nodules on the extremities and occasionally on the trunk. The histopathological findings establishing the diagnosis in these patients centered on the presence of atypical CD3-positive/CD8-positive lymphocytic infiltration, as noted here.[2,4-6] Studies in which T-cell receptor polymerase chain reaction was performed similarly documented clonal proliferation.[5,6] Of note, many patients with reported CD8-positive GCTCL had underlying immunodeficiency, including common variable immunodeficiency, acquired immunodeficiency syndrome, and X-linked agammaglobulinemia; this association is postulated to stem from a predisposition to granuloma formation in these disease states.[5,6] No immunodeficiency preceding the onset of symptoms was identified in this patient after extensive evaluation.

A case series of CD8-positive GCTCL identified lung granulomas in all 4 cases reported.[5] One patient also developed bilateral metacarpophalangeal joint destructive arthritis, demonstrating the potential systemic manifestations of GCTCL.[5] However, it is unclear whether the present patient's pulmonary symptoms and arthritis are related to GCTCL.

Psoralen plus UV-A therapy has been successful in multiple patients with GCTCL and in 2 patients with CD8-positive GCTCL.[2-4] Other options may include methotrexate, bexarotene, and total skin electron beam therapy.

ARTICLE INFORMATION

Author Affiliations: Perelman School of Medicine, University of Pennsylvania, Philadelphia (Stephens); Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Haun, Micheletti).

Corresponding Author: Robert G. Micheletti, MD, Perelman Center for Advanced Medicine, 3400 Civic Center Blvd, South Tower, 7th Floor, Room 724, Philadelphia, PA 19104 (robert.micheletti@uphs.upenn.edu).

Published Online: September 25, 2019. doi:10.1001/jamadermatol.2019.2949

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the patient for granting permission to publish this information.

Self-assessment Credit: This article is eligible for journal-based self-assessment (1 credit) for Maintenance of Certification (MOC) from the American Board of Dermatology (ABD). After completion of an activity, please log on to the ABD website at www.abderm.org to register your credits. This may be done after each exercise or after accumulating many credits.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785. doi:10.1182/blood-2004-09-3502

2. Ishida M, Hotta M, Takikita-Suzuki M, Kojima F, Okabe H. CD8-positive granulomatous mycosis fungoides: a case report with review of the literature. *J Cutan Pathol*. 2010;37(10):1072-1076. doi:10.1111/j.1600-0560.2010.01577.x

3. Mizuno K, Suzuki A, Kato N, Isei T, Okamoto H. CD8-positive granulomatous mycosis fungoides mimicking generalized granuloma annulare. *J Dermatol*. 2012;39(12):1068-1069. doi:10.1111/j.1346-8138.2012.01657.x

4. Kempf W, Ostheeren-Michaelis S, Paulli M, et al; Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer. Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC). *Arch Dermatol*. 2008;144(12):1609-1617. doi:10.1001/archdermatol.2008.46

5. Gammon B, Robson A, Deonizio J, Arkin L, Guitart J. CD8(+) granulomatous cutaneous T-cell lymphoma: a potential association with immunodeficiency. *J Am Acad Dermatol*. 2014;71(3):555-560. doi:10.1016/j.jaad.2014.03.028

6. Rozas-Muñoz E, Mozos A, Pujol RM, et al. Cytotoxic CD8+ granulomatous cutaneous t-cell lymphoma associated with human immunodeficiency virus infection: a diagnostic challenge. *Am J Dermatopathol*. 2018;40(9):707-709. doi:10.1097/DAD.0000000000001026