A case of lymphomatoid granulomatosis presenting with cutaneous lesions

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Key words: B-cell lymphoproliferative disorder; Epstein-Barr virus (EBV)-encoded RNA in situ hybridization; lymphomatoid granulomatosis.

INTRODUCTION

Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder that involves the skin in approximately 50% of cases. We describe a patient with LYG who first presented with cutaneous lesions. His skin biopsy failed to show large B-cell lymphocytes positive for Epstein-Barr virus (EBV)-encoded RNA in situ hybridization (EBER-ISH), highlighting the diagnostic challenges that dermatologists may face when encountering cutaneous LYG.

Abbreviations used:

CT:	computed tomography
EBER-ISH:	Epstein-Barr virus—encoded RNA in situ hybridization
EBV:	Epstein-Barr virus
LYG:	lymphomatoid granulomatosis

CASE REPORT

A previously healthy 28-year-old man presented with recurrent nontender, erythematous skin lesions lasting several months, associated with intermittent fever, weight loss, and cough of 1-month duration. Prior workup included a punch biopsy by an outside dermatologist interpreted as granulomatous dermatitis, chest computed tomography (CT) showing bilateral noncalcified pulmonary nodules, a nondiagnostic CT-guided lung biopsy, and a normal bone marrow biopsy.

On examination, he had multiple nontender, subcutaneous nodules and nummular erythema (Fig 1) scattered throughout the trunk and upper and lower extremities. Skin biopsy findings showed an atypical dense dermal lymphohistiocytic infiltrate predominantly surrounding the blood vessels (Fig 2). Immunohistochemical staining found an infiltrate of predominantly $CD4^+$ lymphocytes; some small $CD20^+$ B cells surrounding blood vessels; and rare $CD30^+$, $CD15^-$ large lymphocytes.

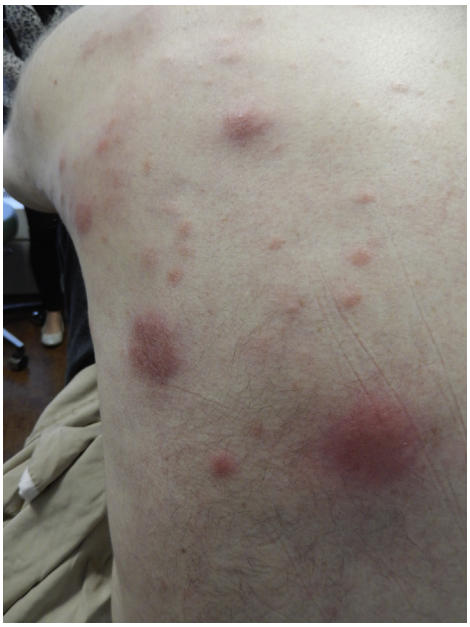

Fig 1. Lymphomatoid granulomatosis as seen on a previously healthy 28-year-old man. Multiple yellowish-red, 3-mm to 4-cm papules and circular plaques over the left back.

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Funding sources: None.
Conflicts of interest: None declared.
This particular case (not manuscript) has been submitted to the 2015 Atlantic Derm Conference Poster Session.

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JAAD Case Reports 2015;1:234-7.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2015.05.008

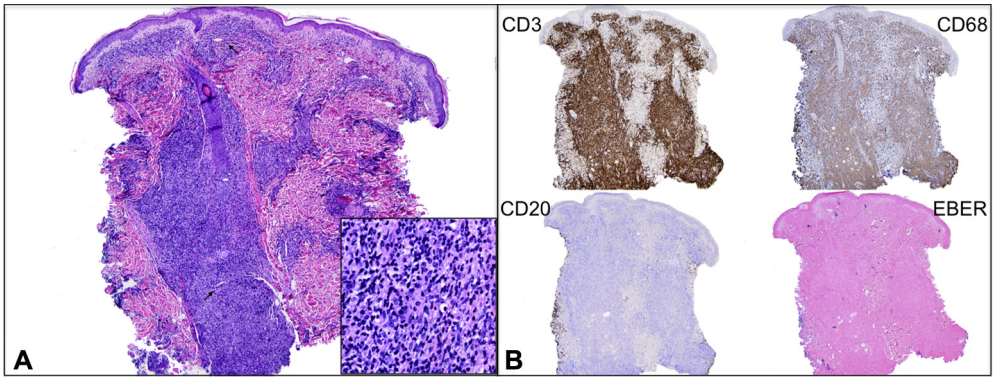

Fig 2. Lymphomatoid granulomatosis as seen on a skin biopsy specimen from the right upper arm. **A**, A dense dermal nodular lymphoid infiltrate surrounding the vessel walls (*black arrows*). Inset shows an inflammatory infiltrate with pleomorphic morphology and consisting of atypical-appearing lymphocytes associated with a few large/transformed cells and a prominent histiocytic component in the background. **B**, Immunohistochemical analysis of skin biopsy shows an infiltrate that is diffusely and strongly positive for CD3, diffusely positive for CD68, very focally and weakly positive for CD20 and negative for EBER-ISH. (**A** and **inset**, Hematoxylin-eosin stain; original magnifications: A, ×4; inset, ×40; **B**, Immunohistochemical staining for CD3, CD68, CD20 antibodies and in-situ hybridization for Epstein-Barr virus-encoded small RNA; original magnification: ×4.)

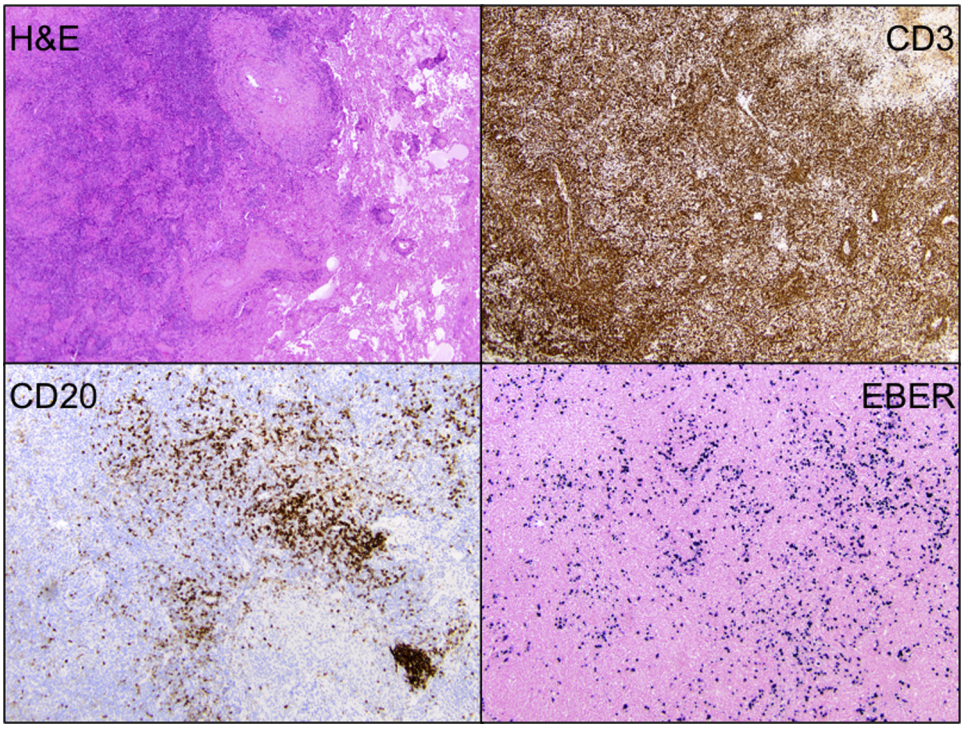

Fig 3. Lymphomatoid granulomatosis as seen on H&E staining and immunohistochemical analysis of lung biopsy. The infiltrate is strongly positive for CD3 and CD20. EBER-ISH is positive in atypical lymphocytes present in lung tissue (EBER positivity is indicated by dark blue staining of the nuclei). (Hematoxylin-eosin stain; original magnification: ×4.)

$CD20^+$ cells were a minor component and results of EBER-ISH were negative. T-cell receptor beta gene rearrangement by florescent polymerase chain reaction showed a polyclonal pattern, militating against a T-cell lymphoproliferative disorder.

Several months later, the patient underwent a lung wedge resection because of worsening constitutional symptoms. Pathologic evaluation of the lung specimen found an atypical lymphohistiocytic infiltrate, with $CD20^+$ lymphocytes, which were

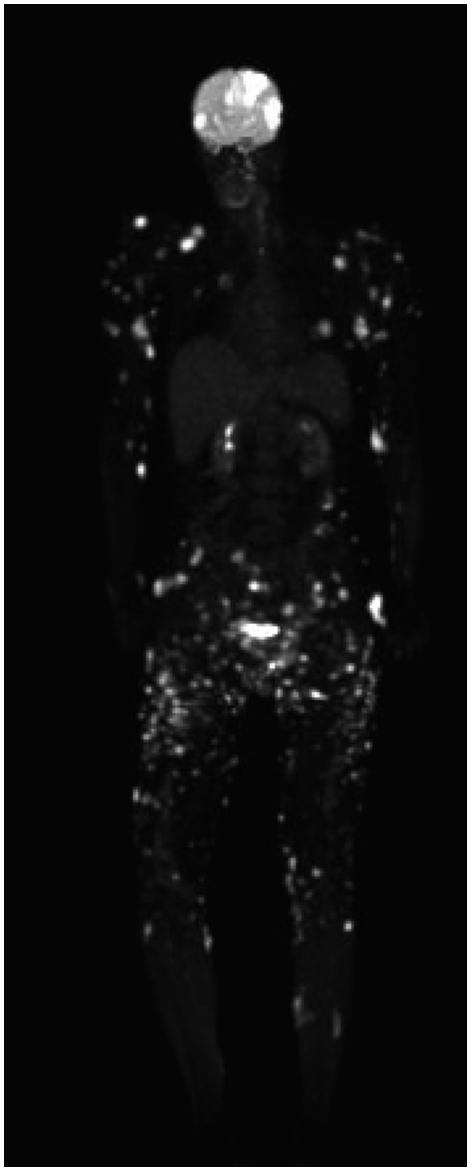

Fig 4. Lymphomatoid granulomatosis as seen on full-body positron emission tomographic/CT imaging shows multiple new fluorodeoxyglucose-avid lesions in the subcutaneous tissue, lungs, and brain.

positive for EBER-ISH (Fig 3). Based on these findings, LYG grade 3 was diagnosed. He underwent 5 cycles of R-EPOCH chemotherapy (rituximab plus infusional etoposide, prednisone, vincristine, and doxorubicin HCL) before presenting again with fever, worsening pulmonary nodules, and new skin lesions.

Over the next several months, the patient's cutaneous lesions worsened. A new aphasia developed, and he was found to have central nervous system lesions on brain magnetic resonance imaging. Full body positron emission tomography/CT is shown in Fig 4. Brain biopsy found pathology similar to that of the skin lesions and negative results for EBER-ISH. The patient was subsequently treated with 26 cycles of whole-brain radiation, interferon alfa, and high-dose rituximab and prednisone but ultimately died of his disease 21 months after receiving his diagnosis of LYG (25 months after first appearance of skin lesions).

DISCUSSION

LYG is a rare EBV-driven B-cell lymphoproliferative disorder that most frequently involves the lungs but may also involve the skin and central nervous system. LYG has a median survival of 14 months, and a large portion of cases eventually progress to overt EBV^+ lymphoma.[1] Presentation can be indolent and highly variable, with constitutional symptoms such as fever, weight loss, and fatigue dominating the clinical picture, followed by more specific symptoms such as cough, dyspnea, and chest pain.[2,3]

Pathologically, LYG is characterized by features of an angioinvasive and angiodestructive lymphohistiocytic infiltrate, with many reactive T cells and few large, atypical monoclonal B cells.[2] Diagnosis is usually made by histologic examination and immunohistochemical staining of a lung biopsy, which shows a mixed mononuclear cell infiltrate containing large B lymphocytes and numerous small T lymphocytes, vascular infiltration, necrosis, and EBER-ISH in B lymphocytes.[4]

Bilateral lung involvement is almost universal, and the skin is the most common extrapulmonary site of involvement of LYG (40% to 50%).[1,5] When a patient with infiltrative cutaneous lesions presents without prior lung imaging, there should be a low threshold for obtaining a chest CT, particularly if respiratory or constitutional symptoms are present. Cutaneous lesions usually present concomitantly with lung nodules, but they may also precede pulmonary involvement or symptoms in up to 10% of cases.[6] Cutaneous lesions may also be the first sign of relapse in an otherwise asymptomatic patient with a prior diagnosis of LYG.[7] The progressive nature of the disease and urgent need for treatment in grades 2 and 3 LYG make it critical to recognize the cutaneous manifestations of LYG.

Cutaneous LYG lesions are polymorphous and may present as erythematous dermal papules, subcutaneous nodules, or indurated and atrophic plaques, with or without ulceration.[3] The differential diagnosis includes granulomatosis with polyangiitis, cutaneous T-cell lymphoma, cutaneous lymphoid hyperplasia, metastatic carcinoma, granuloma annulare, Hansen's disease, and sarcoidosis. Skin biopsies mirror most of the histologic findings seen

on lung biopsy but frequently lack $CD20^+$ B cells or EBER-ISH positivity, 2 important features of LYG almost always detected in pulmonary lesions.[8] Detection of EBV-encoded RNA on skin biopsy is more likely to be present in nodular lesions than papules or plaques.[3] Nevertheless, even cutaneous nodules of LYG have been found to be EBER-ISH negative.[9]

Although our patient's skin biopsy was inconclusive and contained very few $CD20^+$ B cells, the histologic findings on pulmonary biopsy were diagnostic of grade 3 LYG, the most severe grade associated with the highest mortality. This case shows how the absence of EBV positivity or large $CD20^+$ B cells on skin biopsy does not exclude LYG as a diagnosis but makes lung biopsy critical to identification of disease. In the absence of a lung biopsy, diagnosis is difficult, and cutaneous LYG may mimic other disease processes, leading to a delay in diagnosis. Moreover, the World Health Organization grading of LYG is based on many of the features frequently absent on skin biopsy, such as the severity of necrosis and EBV positivity, further highlighting the importance of obtaining a lung biopsy.[10] In the extremely rare case of LYG without pulmonary involvement, dermatologists may have to rely on skin biopsy findings to help with diagnosis. In skin biopsy specimens with EBER-ISH positivity, dermatopathologists should perform additional immunohistochemical stains ($CD56^+$, cytoplasmic $CD3\varepsilon^+$) to rule out natural killer/T-cell lymphoma.[3]

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