

Smoldering cutaneous course of lymphomatoid granulomatosis



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Key words: lymphomatoid granulomatosis.

INTRODUCTION

Lymphomatoid granulomatosis (LyG) is a rare, angioinvasive, positive for Epstein-Barr virus (EBV), B-cell lymphoproliferative disorder with a predilection for the lungs.^{1,2} While cutaneous involvement in LyG is not particularly uncommon, we report a remarkable case of high grade LyG, which presented as an indolent cutaneous disorder in an otherwise healthy 59-year-old female, at least 6 years before diagnosis. Upon presentation our patient had a long history of recurrent crops of infiltrative papules and nodules that had never resulted in clear histologic or clinical diagnoses. Grade 3/3 LyG was ultimately diagnosed after biopsy specimen of a new isolated, enlarging subcutaneous nodule on the left buttock. Review of all prior biopsy specimens revealed findings consistent with LyG. LyG has been reported to mimic other dermatologic disorders both clinically and histologically.^{1,2} We find our patient's chronic, relapsing course, lack of systemic symptoms and skin-predominate presentation particularly notable.

CASE REPORT

A 59-year-old Caucasian woman with a history of granuloma annulare presented in 2010 with bilateral, lower-extremity, cutaneous lesions. A biopsy specimen showed a septal panniculitis most consistent with erythema nodosum. A second biopsy showed a lobular panniculitis with primarily granulomatous inflammation without vasculitis. These lesions ultimately resolved in late 2011, after prednisone and dapsone therapy. Subsequently, in December 2015, she developed a new, pruritic,

Abbreviations used:

CT: computed tomography
 EBV: Epstein-Barr virus
 LyG: lymphomatoid granulomatosis
 PET: positron emission tomography

tender, scaly rash on the right arm. A biopsy specimen revealed a nonspecific granulomatous dermatitis of unknown etiology without typical features of granuloma annulare. This lesion resolved with topical steroid use.

In June 2016, she again presented with a new, enlarging, tender, subcutaneous nodule without ulceration or drainage. She was otherwise asymptomatic, without any shortness of breath, cough, fever, or weight loss. On physical examination, she had a single, firm, 5-cm × 3.5-cm nodule located on the left buttock (Fig 1).

Histologic evaluation revealed the involvement of the dermis and subcutis, with an atypical lymphocytic proliferation admixed with abundant macrophages surrounding an extensive area of necrosis, with foci of the atypical lymphocytes involving vessels (Fig 2). The atypical lymphocytes were reactive for CD20 and CD30. The T cells were reactive for CD3, CD4, and CD5 staining. In situ hybridization for EBV was positive in the tumor, while the serum EBV viral load was negative. The patient was diagnosed with an atypical lymphoid infiltrate, positive for EBV, with extensive necrosis (Fig 3). The subcutaneous nodule on the left buttock regrew within a few months. Repeat biopsy

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2022;21:66-9.

2352-5126

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<https://doi.org/10.1016/j.jcdr.2021.12.010>



Fig 1. Left buttock. Firm, somewhat tender, 5-cm × 3.5-cm, subcutaneous nodule; no overlying epidermal change.

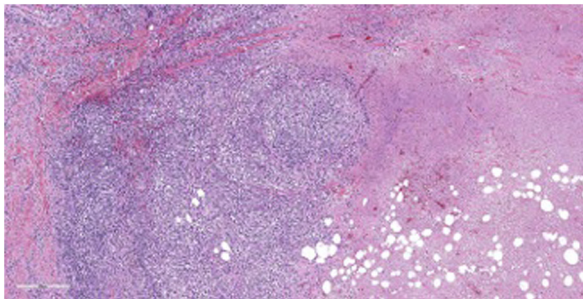


Fig 2. Lymphoma granulomatosis. Atypical lymphocytic proliferation admixed with abundant macrophages surrounding an extensive area of necrosis. There are foci of atypical lymphocytes involving vessels. (Hematoxylin and eosin stain; original magnification: ×80.)

pathology led to a diagnosis of LyG, grade 3 of 3. Importantly, all of her prior biopsies since 2010 were reviewed, and, in retrospect, all were consistent with cutaneous LyG.

A whole-body positron emission tomography (PET)/computed tomography (CT) scan showed an avid subcutaneous nodule on the left buttock and innumerable tiny pulmonary nodules, nonavid and too small to characterize. The patient was referred to pulmonology, and the decision was made to repeat the CT scan in 6 months given her lack of pulmonary symptoms. Repeat PET/CT showed the pulmonary nodules had increased in size and number, with some showing avidity. No biopsy was performed due to patient preference, because the nodules were thought to most likely be due to LyG.

Systemic chemotherapy was initiated, with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. A posttreatment PET scan in November 2017 showed resolution of the buttock lesions and the pulmonary nodules. In August 2018, the patient presented with a new, firm, mobile nodule on the right forearm. A biopsy showed recurrent LyG. A whole-body PET/CT scan showed innumerable hypermetabolic subcutaneous

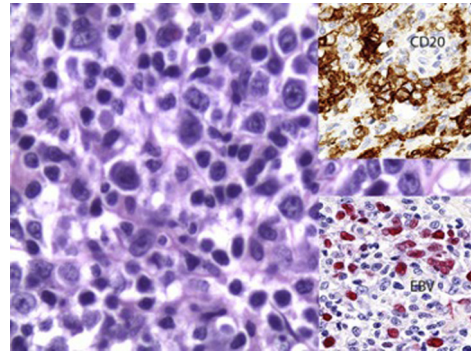


Fig 3. Lymphomatoid granulomatosis. The lymphocytes are large, with striking nuclear pleomorphism (*left*, hematoxylin and eosin stain; original magnification: ×40). The large, malignant lymphocytes are CD20⁺ (*upper right*, CD20 immunostain Diaminobenzidine; original magnification: ×40.) In situ hybridization with Epstein-Barr virus–encoded small RNA probe showed many of the large, malignant lymphocytes had reactivity for Epstein-Barr virus, with >50 positive cells per high-power field (*lower right*, in situ hybridization, Epstein-Barr virus; original magnification: ×40). EBV, Epstein-Barr virus.

nodules, lymph nodes, right hepatic lobe hypodensities, and multiple osseous lesions (Fig 4). Despite dramatic systemic recurrence, she continued to be asymptomatic. She received one dose of brentuximab vedotin, with almost complete clearance of the subcutaneous nodules; however, repeat imaging showed progression of the disease in her lungs. Therefore, therapy was switched to obinutuzumab plus gemcitabine, dexamethasone, and cisplatin. She achieved a complete response to therapy after 3 cycles of obinutuzumab plus gemcitabine, dexamethasone, and cisplatin. In January 2019, she received an autologous stem cell transplant. Twenty-seven months later, she is still disease-free.

DISCUSSION

LyG is a rare, angioinvasive, positive for EBV, B-cell lymphoproliferative disorder that typically presents as a multisystem disease with a predilection for the lungs. A third of patients will have concurrent cutaneous involvement at diagnosis.^{1,2} However, in 10% to 15% of cases, cutaneous involvement can occur prior to the development of pulmonary lesions, although usually only a few months earlier.^{3,4} There are few reports of LyG without lung involvement, and even fewer cases of LyG presenting as a skin-limited disease, in the literature.⁵⁻⁷ While our patient may have had pulmonary involvement, the majority of her disease was subcutaneous nodules that were present years before disease progression, requiring systemic therapy. Her presentation of primarily cutaneous involvement and a prolonged disease course is felt to be

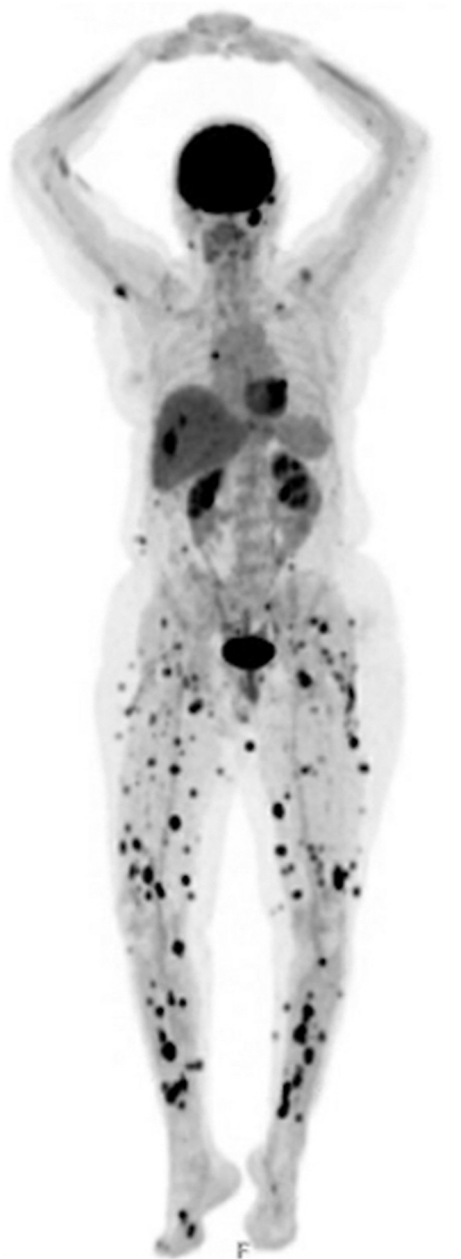


Fig 4. Whole-body positron emission tomography/computerized tomography scan, September 2018, showed recurrence with innumerable hypermetabolic subcutaneous soft tissue nodules, lymph nodes, right hepatic lobe hypodensities, and multiple osseous lesions.

exceptionally rare, especially in the setting of a histologic grade of 3 at the time of diagnosis.

LyG has been reported to mimic other diseases, such as sarcoidosis or other granulomatous diseases and vasculitis (especially granulomatous vasculitis), both clinically and histologically.^{1,2} For diagnosis, the following 3 histologic findings must be present: (1) mixed mononuclear cell infiltrate containing large and small lymphoid cells comprised of T cells, plasma

cells, and histiocytes; (2) variable numbers of CD20⁺ large B cells, often with atypia, within a background of CD3⁺ small lymphocytes; and (3) the angiocentric or angioinvasive accumulation of lymphocytes.^{7,8} In addition, supportive findings for diagnosis that are not always present include cellular infiltrate necrosis; positive in situ hybridization for EBV; and radiologic findings with multiple nodules involving the lung, skin, or nervous system.⁷ Despite this, due to the scarcity of cutaneous B lymphocytes, in situ hybridization for EBV may be negative in skin specimens.

Our patient had a long history of recurrent crops of infiltrative papules and nodules that had previously been diagnosed as granuloma annulare and erythema nodosum, respectively. After her diagnosis of LyG in 2016, a review of all biopsies since 2010 revealed findings consistent with LyG, demonstrating an indolent disease process occurring intermittently over the 6 years prior to the LyG diagnosis.

LyG has, rarely, been reported to have a chronic, cyclic disease course that can exhibit subcutaneous, dermal, and epidermal presentations that heal spontaneously, with or without residual scarring.^{4,9} However, overall, this is atypical for LyG, so we found our patient's chronic course particularly notable.

In conclusion, although primarily a disease of the lungs, LyG can present initially in the skin and may have diverse dermatologic manifestations that mimic a number of other, more common cutaneous disorders. The clinical behavior of LyG can vary widely, from spontaneous remission to behaving as an aggressive large-cell lymphoma. This case demonstrates that some patients with a skin-only presentation can do well for years with skin-directed therapies. However, the transformation to a more aggressive phenotype may eventually occur. At that time, aggressive chemotherapy can lead to a durable remission.

Conflicts of interest

None disclosed.

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