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Case Presentation

An eschar and violaceous nodules as the presenting signs of lymphomatoid granulomatosis

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Abstract

Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder associated with infection by Epstein-Barr virus (EBV). The lung is the most common site of involvement, but LYG may initially manifest in the skin. LYG has been associated with immune dysregulation. Treatment regimens are not well-defined, but clinical trials targeting EBV have been successful. We report a 31-year-old male with LYG who presented with cutaneous symptoms. The skin biopsy was devoid of B-cells and non-reactive for EBV. We present this case to emphasize the role of dermatologists in the diagnosis of LYG and to caution clinicians that cutaneous lesions may lack diagnostic evidence of EBV infection.

Keywords: lymphomatoid granulomatosis; LyG; EBV; Epstein Barr; virus; eschar; nodule; violaceous; lymphoma; skin

Case synopsis

A 31-year-old man with no significant past medical history presented to the dermatology clinic with a six-month history of tender violaceous plaques across the abdomen and all extremities. The patient described two lesions that developed a white-gray overgrowth and subsequently turned black. Review of systems was positive for fatigue, malaise, sweats, proximal myalgias in the shoulders and thighs, leg swelling, occasional dysesthesias over the back, thighs, and legs, and an eighty-pound intentional weight loss. Physical exam revealed numerous violaceous plaques and nodules across the forearms, abdomen, and legs (Figures 1,2). There was a 3-cm necrotic ulcer across the left anterior shin (Figure 3). Clinical differential diagnosis included vasculitis, deep fungal infection, mycobacteriosis, and lymphoma. A 5-mm punch biopsy was obtained and the patient was referred to the hematology/oncology department for further systemic workup.

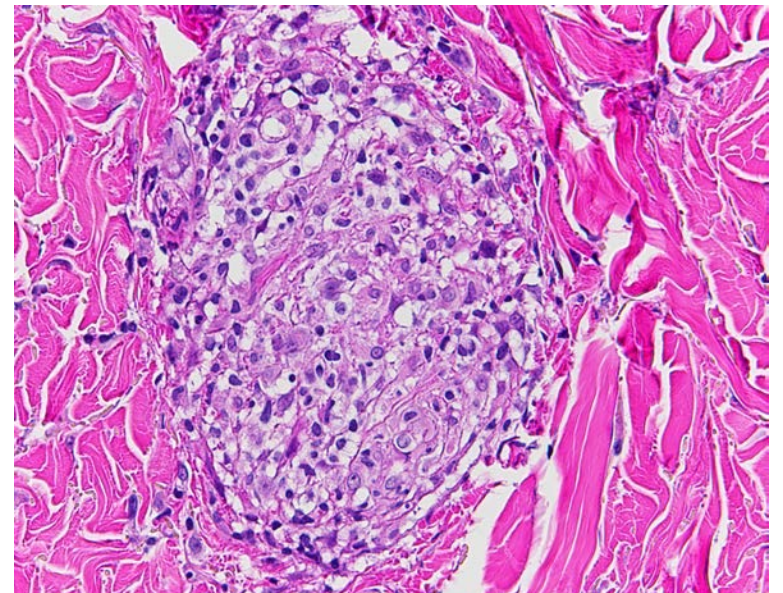
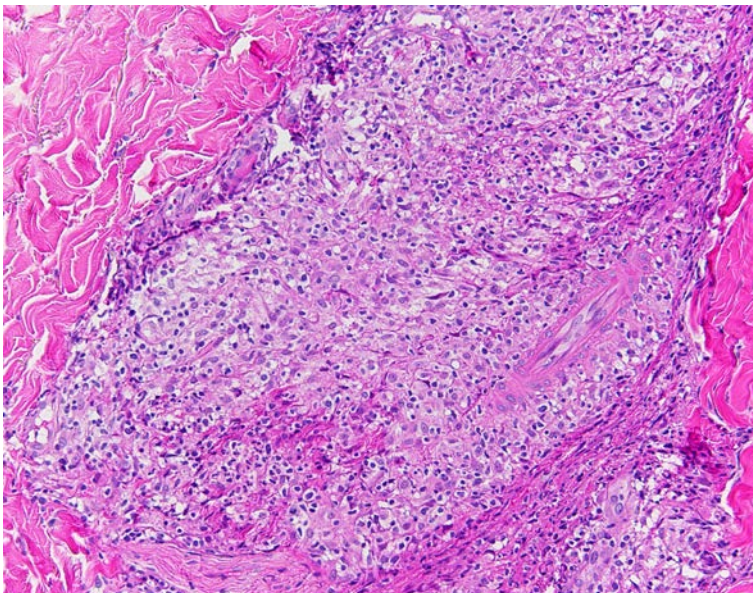
Punch biopsy of a ventral forearm plaque demonstrated perivascular expansile nodules comprised of CD163⁺histiocytes and CD3⁺T-cells. The infiltrate resembled perivascular granulomas. CD20 immunostaining was negative for B-cells and in situ hybridization for Epstein-Barr virus was non-reactive (Figures 4-7). Pertinent labs included an elevated AST/ALT ratio of 115/111, an elevated C-reactive protein at 5.75 mg/dL, and an elevated creatine kinase at 698 U/L. Computed tomography scan demonstrated numerous pulmonary nodules and masses, moderate hepatosplenomegaly with multiple hypodense hepatic lesions, diffuse lymphadenopathy, and innumerable subcutaneous nodules. Lung biopsy demonstrated an atypical B-cell infiltrate with strong Epstein-Barr virus expression by in situ hybridization. We diagnosed grade 3 LYG.



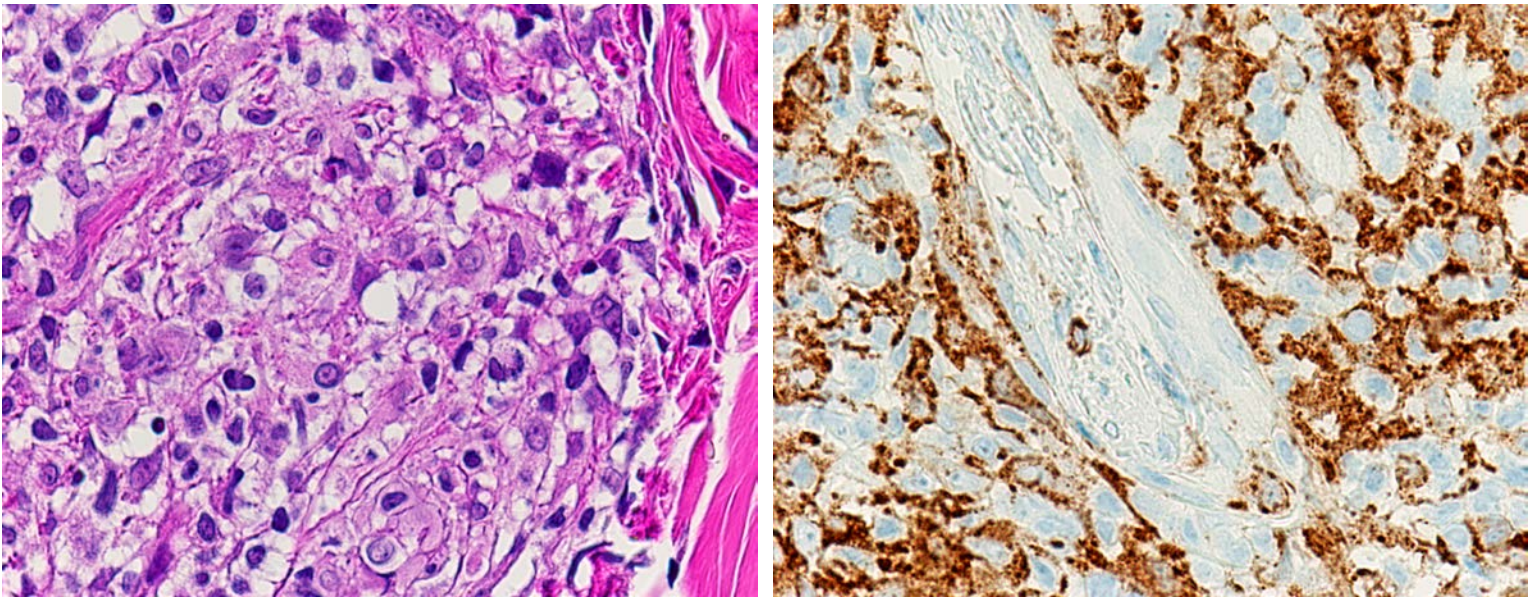
Figures 1 and 2 Violaceous nodules and plaques



Figure 3 Ulcerated, violaceous plaque



Figures 4 and 5



Figures 6 and 7

Discussion

Lymphomatoid granulomatosis (LYG) is a rare multisystem B-cell lymphoproliferative disorder with a median survival rate of fourteen months [1]. First described by Liebow *et al.* in 1972, LYG primarily affects the lungs, but may also afflict the integumentary, renal, hepatic, and nervous systems [2]. It typically occurs in middle-aged adult males and mortality rates can reach as high as 75% within two years [1]. Skin lesions are the most common extrapulmonary findings and may be the first sign of presenting illness in one third of patients, preceding lung involvement by a variable period of two weeks to nine years [3]. Cutaneous LYG manifests as dermal or subcutaneous nodules with or without accompanying ulcerative plaques. Additional skin lesions include indurated plaques, macules, papules, and annular lesions varying in color from tan to erythematous to violaceous [4,5].

The pathogenesis of LYG is associated with Epstein-Barr virus (EBV) infection, which is thought to drive the formation of atypical clonal B-cells through complex molecular interactions [6]. Although EBV is identified in the vast majority of lung biopsies, it is only found in 14% to 37.5% of skin biopsies [1,4,7]. Hence, systemic work-up may be necessary for accurate diagnosis.

Immune dysregulation may play a role in pathogenesis. LYG has been reported in patients with autoimmune illnesses such as rheumatoid arthritis, sarcoidosis, and Sjogren syndrome, infections such as HIV and chronic hepatitis, congenital immunodeficiencies such as Wiskott-Aldrich syndrome and X-linked lymphoproliferative syndrome, post-organ transplant immunodeficiency [6,8], and other hematologic malignancies [9,10]. There was no evidence of immune dysregulation in our patient.

LYG portends a grave prognosis. Optimal treatment remains to be defined, but most patients are treated with chemotherapy. The association of LYG with EBV is well-known, and clinical trials targeting this pathogenesis with interferon- α 2b have shown some success in patients with low grade LYG [11].

Our patient underwent a challenging treatment course. Initially, he received two rounds of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. After two months, treatment response was suboptimal as portrayed by progression of disease on positron emission tomography scan. He then underwent high-dose methotrexate and cytarabine therapy, which resulted in partial response. The next regimen included peripheral stem cell transplant from his human leukocyte antigen identical brother after myeloablative therapy with etoposide, cyclophosphamide, and total body irradiation. Six months post bone marrow transplant, the patient entered disease remission, but battled complications of graft-versus-host disease and repeated pulmonary infections.

Conclusion

Our case illustrates that nonspecific cutaneous findings may serve as the initial presenting complaint in LYG. Clinicians should be aware that patients who present with cutaneous symptoms may lack diagnostic evidence of B-cell infiltration of the skin and have skin biopsies that are non-reactive for EBV. Systemic work-up is necessary for such patients.

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