Lymphomatoid Granulomatosis: A Diagnostic Challenge

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Abstract: Lymphomatoid granulomatosis is a rare Epstein barr virus associated lymphoma. It most commonly involves lungs, skin, central nervous system and kidneys. When lungs are involved, it often mimics common pulmonary conditions like pneumonia, making diagnosis extremely challenging. We present one such interesting case of Lymphomatoid granulomatosis in an immunocompetent young man.

Keywords: Lymphomatoid granulomatosis, EBV.

INTRODUCTION

Lymphomatoid granulomatosis(LYG) is an extremely rare lymphoproliferative process associated with Epstein barr virus infection. Lungs are almost always involved and pulmonary LYG is often confused for pneumonia and other common lung conditions posing a diagnostic conundrum.

CASE DESCRIPTION

In October 2012, a 28 year old perfectly healthy young man presented to a dermatologist with erythematous, raised, painful, circumscribed lesions over his left flank and left lateral chest wall. He was felt to have some kind of "contact dermatitis" and was prescribed topical steroids. Rash responded to steroids but returned shortly after stopping them. Besides the rash, he also reported a new symptom of non-productive cough with mild dyspnea. He also started to develop fever, chills, night sweats, loss of appetite and unintentional weight loss. He was admitted to an outside hospital for further evaluation.

A punch biopsy of skin lesion revealed granulomatous dermatitis. A chest radiograph revealed multiple masses involving both lungs, the largest of them involving right upper lobe, measuring 4.7 cm in its greatest diameter. A computerized tomography of chest confirmed the findings from the chest x-ray. No cavitation or calcification of these lesions was identified, and no pleural effusion or mediastinal lymphadenopathy was noted. A testicular ultrasound was performed which eliminated the possibility of testicular cancer as the primary underlying malignancy. A CT-guided biopsy of the lung lesion revealed necrotic acellular material with negative bacterial, acid fast bacilli (AFB) and fungal cultures. Patient was empirically treated with a five week course of antibiotics for presumed infection. Hepatitis B and C serologic testing and HIV screening were negative. Epstein Barr virus nuclear antigen (EBNA) IgG antibody titer was >8.0 (<0.9 is negative) and EBV capsid antigen (EBV-VCA) IgG was >8.0 (<0.9 is negative), while EBV early antigen diffuse complex (Ea-D) was 0.8 (<0.9 is negative) and EBV-VCA IgM was <0.2 (<0.9 is negative). This EBV panel was interpreted to be consistent with past infection with Epstein Barr virus. A bone marrow aspiration and biopsy revealed normocellular marrow with no evidence of lymphoma on flow cytometry.

After discharge from the hospital, he was evaluated by another dermatologist who performed a deep excisional biopsy of a skin lesion on his left lower back, which revealed dense lymphocytic infiltration with extensive CD3 positive T-cell infiltrate and few B-cells reminiscent of Reed-sternberg cells staining strongly for CD30, CD20 and LCA with rare CD15 positive cells. These findings were felt to be consistent with his previous diagnosis of 'granulomatous dermatitis'.

Three months into the diagnostic work up, the patient at this time presented to our lymphoma clinic for consultation. A repeat punch biopsy of skin and a wedge resection of left upper lobe lung lesion were performed. Skin biopsy was not informative. However, the lung biopsy was significant for atypical polymorphic lymphohistiocytic infiltrates with angiocentricity and necrosis. These atypical cells were positive for CD20, CD30, PAX5 and strongly positive for EBV encoded RNA on insitu hybridization (EBER-ISH). Numerous

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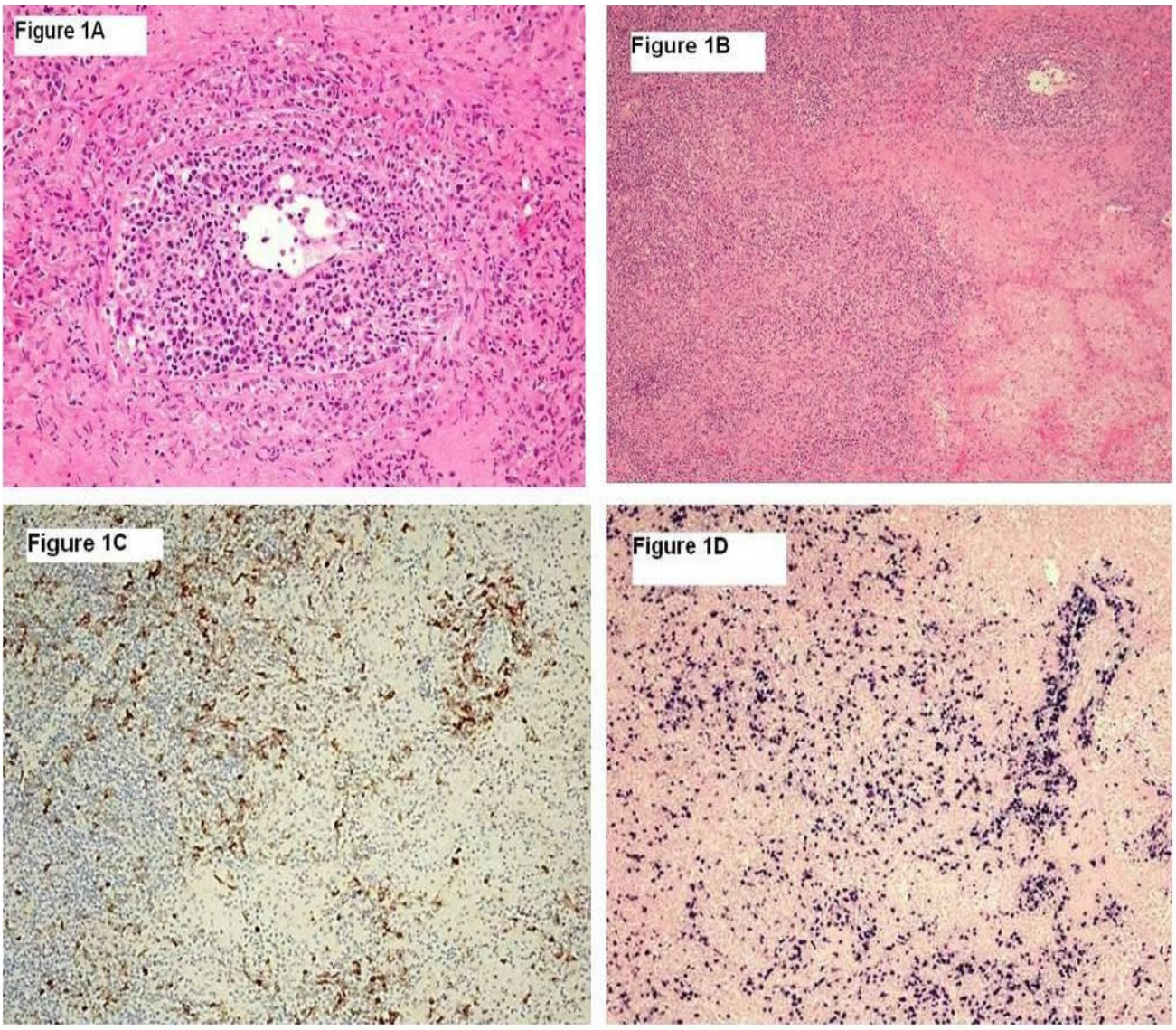

Figure 1: Histologic sections of the lung wedge biopsy demonstrate pulmonary parenchyma with an atypical lymphoistiocytic in filtrate encircling segmental areas of infarct-like necrosis. Foci with transmural vascular invasion and associated angiodestruction are present. (Fig. **1A** and Fig. **1B**: H&E stain)
Variable numbers of CD20 positive B-cells (Fig. **1C:** CD20 imunohistochemical stain) are identified admixed with in the infiltrate with abundant atypical EBV+ B –cells found palisading around the necrotic tumor and with in the vasculitic lesions (Fig. **1D**: in situ hybridization for EBV-encoded RNA). EBER+ cells were enumerated at >50 per high power field (LYG, grade 3).

CD2, CD3 positive T cells were found in the back-ground (Figure **1**). The patient was diagnosed with lymphomatoid granulomatosis (LYG) grade 3.

The patient was started on combination chemo immunotherapy with rituximab, etoposide, vincristine, cyclophosphamide and adriamycin (R-EPOCH). After completing six cycles, he had an excellent response initially with a dramatic improvement in his skin lesions as well as a complete resolution of his pulmonary symptoms. However, very shortly he developed respiratory distress requiring admission to intensive care unit showing worsening pulmonary findings on imaging studies and necrotic elements seen on broncho scope, along with worsening skin findings. Work up for infectious causes again has been negative and patient is currently started on a trial with interferon.

DISCUSSION

Lymphomatoid granulomatosis is a very rare angiodestructive lymphoproliferative disorder. It was first described by Liebow *et al.* in 1972 as an uncommon multi-organ systemic disease [1]. The World Health Organization classification in 2008 described LYG as an extranodal, angiocentric, T-cell

rich B-cell lymphoma and placed it under the category of "Large B-cell Lymphomas"[2]. It is an EBV driven lymphoproliferative process. Lungs are almost always involved and the other common sites of involvement are skin, central nervous system and kidneys [3, 4]. Lymphoid organs and spleen are usually spared at the time of diagnosis [3, 4]. Pulmonary LYG mimics the common pulmonary conditions like pneumonia, and the distinction between them can be extremely difficult as LYG is not routinely considered in the initial differential diagnoses [5]. Cutaneous manifestations are quite variable from erythematous maculopapular eruptions to subcutaneous nodules that may ulcerate and sometimes, may present as indurated plaques. As seen in our patient, skin biopsies usually lack the abnormal EBV positive B-cells making the diagnosis extremely challenging. However, lung biopsies are typically diagnostic [4, 5]. Serological testing for EBV has been found to be positive in almost all the cases.

Histological features of polymorphic lymphocytic infiltrate, angiocentricity and marked transmural infiltration of the blood vessels, along with varying degree of central necrosis are required for the definitive diagnosis of LYG [3] Based on the proportion of EBV positive B cells, LYG is divided into three grades [3, 4]. There is no standard therapeutic approach to this lymphoma. However, the study from the NCI recommends using interferon alpha-2b for low grade LYG (grade 1 and 2) and dose adjusted R-EPOCH for high grade (grade 3) LYG [4, 6].

CONCLUSION

Lymphomatoid granulomatosis is an extremely rare EBV driven lymphoproliferative disease with multi-organ involvement. Diagnosis is often a big challenge, firstly because of its close resemblance to many common diseases, and secondly because physicians often do not consider LYG in their initial differential diagnoses and therefore, fail to look for EBV serology or EBV-ISH on biopsies. Skin biopsies are not always diagnostic and lung biopsies should be obtained in such cases. Patients with low grade LYG can be observed for regression and interferon-alpha-2b can be used to enhance the host's immune system. High grade LYG should be treated immediately with combination chemotherapy and rituximab, similar to those used in diffuse large B cell lymphoma.

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