Fever, Dry Cough and Exertional Dyspnea: Pulmonary Lymphomatoid Granulomatosis Masquerading as Pneumonia, Granulomatosis with Polyangiitis and Infectious Mononucleosis

Bin Xu¹, Hui Liu², Bishi Wang³, Hongwei Zhang¹, Hao Wu¹, Ronghua Jin¹ and Yulin Zhang¹

Abstract

Lymphomatoid granulomatosis (LYG) is a rare Epstein-Barr virus-associated lymphoproliferative disorder. The disease lacks specific clinical and radiological manifestations, which may delay a definitive diagnosis. We report the case of a 39-year-old man with pulmonary LYG who presented to a hospital after experiencing three months of fever, weight loss, dry cough and exertional dyspnea. He was initially misdiagnosed with pneumonia, granulomatosis with polyangiitis and infectious mononucleosis due to the non-specific manifestations of the disease. We herein present the clinical and radiological characteristics of this case and discuss the procedure for pathological diagnosis, which will likely help clinicians in making a timely definitive diagnosis of this disease.

Key words: lymphomatoid granulomatosis, misdiagnosis, pulmonary, Epstein-Barr virus

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Introduction

Lymphomatoid granulomatosis (LYG), which was first described in 1972 by Liebow, is a rare Epstein-Barr virus (EBV)-associated lymphoproliferative disorder (1). Most of the literature on this disease consists of case reports. LYG is an angiocentric and angiodestructive process that most commonly affects the lung as a bilateral nodular infiltrate composed of EBV-positive B cells admixed predominantly with reactive T cells. The disorder’s lack of true granulomatous features (2), results in protean manifestations in both the clinical and radiological findings, which may delay a definitive diagnosis (3, 4).

We herein report a case of EBV-associated pulmonary lymphomatoid granulomatosis (PLG) that was initially misdiagnosed as pneumonia, granulomatosis with polyangiitis and infectious mononucleosis due to the patient’s non-specific clinical presentation.

Case Report

A 39-year-old man complained of a 3-month history of fever (axillary temperature: 37.5-40°C), weight loss of 15 kg, a dry cough and mild exertional dyspnea. His past medical history included 1 week of fever (an axillary temperature of approximately 38.5°C) and bilateral submandibular lymph node swelling that had occurred more than 3 months prior to his presentation. His symptoms strongly suggested an acute EBV infection, but the patient had no history of human immunodeficiency virus (HIV) infection, chronic liver disease, autoimmune disease, malignancy, organ transplantor treatment with immunosuppressive drugs. A physical examination revealed a subcutaneous nodule of 1.5×1.0 cm in diameter in the right cervical region and some fine rales were heard from the bottom of the right lung. The systemic ex-
was subsequently adopted, but the patient’s symptoms a later examination was otherwise unremarkable. Laboratory tests revealed that the patient was negative for anti-EBV-EA and anti-EBV-VCA IgM antibodies. However, a test for serum anti-EBV IgG antibody was positive. The patient’s plasma EBV DNA level was 25,900 copies per mL. The results of laboratory tests taken on admission are shown in Table.

The patient was initially suspected to have a blood disease due to his fever and swollen lymph nodes. Therefore, an examination of the bone marrow morphology and a biopsy of the right cervical lymph node were performed. Hemophagocytosis was found in the bone marrow (Fig. 1A), and the lymph node histology revealed a large number of proliferative lymphocytes and complete structural deterioration. However, hematological malignancy could not be confirmed. Infectious mononucleosis was also considered because of the presence of fever, lymph node swelling, anti-EBV IgG antibody seropositivity and the presence of detectable plasma EBV DNA. However, the negative anti-EBV-EA and anti-EBV-VCA IgM antibody findings did not support a new EBV infection. Bronchoscopy revealed a normal bronchial mucosa (Fig. 1B, C). Bronchoalveolar lavage was performed. The patient’s alveolar lavage fluid culture and acid-fast staining showed no signs of bacteria, fungi or tubercle bacillus infection. A thoracic CT scan revealed scattered nodules in both lungs (severe in the right lung) (Fig. 2A-D), but swollen lymph nodes were not observed in the mediastinum. Based on the clinical symptoms and chest imaging, the patient was tentatively diagnosed with a pulmonary infection, and tuberculosis was rapidly excluded following a negative PPD test and alveolar lavage fluid acid-fast staining. Empirical antibiotic therapy (including antifungal) was subsequently adopted, but the patient’s symptoms failed to improve. To confirm the diagnosis, a percutaneous lung needle biopsy was performed at this time, revealing nodular polymorphic lymphoid infiltration and vascular wall necrosis, which indicated a diagnosis of granulomatosis with polyangiitis. Consequently, a course of corticosteroids was selected as the experimental treatment. Although two weeks of corticosteroid therapy significantly improved the patient’s complaints of fever, dry cough and dyspnea, his radiological presentation deteriorated (Fig. 2E-L). Ultimately, a second percutaneous needle aspiration biopsy of the right lung lesion was performed. The histology revealed necrotic angitis with endothelial cell swelling and vascular wall necrosis, and a nodular polymorphous mononuclear extravasate containing large numbers of small lymphocytes and scattered atypical large cells (Fig. 1D, E). Special staining revealed that the atypical large cells included CD20-positive B cells (Fig. 1F). CD3 and CD4 markers characterized a large number of reactive T-cells (Fig. 1H, I). An EBV in situ hybridization procedure revealed EBV among the scattered atypical large cells (Fig. 1G). This finding was consistent with a diagnosis of lymphomatoid granulomatosis, grade 2.

The patient was treated with methylprednisolone, cyclophosphamide and vinblastine. His complaints of fever, dry cough and dyspnea began to improve in the second week of chemotherapy. However, 4 weeks later there was a rapid exacerbation of the patient’s symptoms of fever, expectoration and dyspnea. He eventually died of pneumonia and respiratory failure. The family declined a post mortem examination.

This case report was approved by the Human Subjects Protection Committees of Beijing You An Hospital, Capital Medical University. Written informed consent was obtained.
usually controlled by immune regulation mediated by cytotoxic T cells. In an immunodeficient state, the defenses of the host may not be able to curb EBV-induced B-cell proliferation (5), even if they have directly developed to diffuse large B-cell lymphoma (6). The positive anti-EBV IgG and plasma EBV DNA observed in the present patient suggested the possibility of PLG or another B cell lymphoproliferative disease.

It is challenging to make a diagnosis of PLG because of its atypical clinical presentation and non-specific radiological presentations, including central low attenuation, ground-glass halo, peripheral enhancement of nodules/masses and an even cavity (6-9), which sometimes masquerades as pneumonia, bronchial carcinoma or other diseases (10-12). It is because of its atypical clinical manifestation that this case was previously misdiagnosed as pneumonia, granulomatosis with polyangiitis, and infectious mononucleosis. Performing histology is essential because it reveals the following characteristics: nodular polymorphic lymphoid infiltrate composed of small lymphocytes, plasma cells, and variable numbers of from the patient.

**Discussion**

Burkitt’s lymphoma and other B cell lymphoproliferative diseases are often observed to be partly associated with EBV infection, which can guide the diagnosis of this disease. LYG, which is a member of the family of B cell lymphoproliferative diseases, is thought to be provoked by EBV infection, particularly due under immunocompromised conditions (5-7). Furthermore, LYG always relapses after successful treatment due to the inability of the immune system to eliminate the disease. Although this patient was not apparently immunocompromised, he had a continuously high serum EBV load. In vitro, EBV has been observed to bind to the complement receptor CD21 on B cells, resulting in the continuous growth or immortalization of infected B cells. In vivo, polyclonal B-cell proliferation occurs but is usually controlled by immune regulation mediated by cyto-

![Figure 1](image_url). Morphological presentation of pulmonary lymphomatoid granulomatosis. A. Hemosphagocytosis in the bone marrow. B, C. Normal bronchial mucosa. D, E. Pathological morphology of a pulmonary biopsy. Angiitis and nodular polymorphous mononuclear infiltrates containing a large number of small lymphocytes and scattered atypical large cells (white arrows denote vascular wall necrosis and red arrows denote scattered atypical lymphocytes, Hematoxylin and Eosin staining). F. An immunohistochemistry stain revealing CD20 positive and scattered atypical large cells (black arrows denote CD20 positive cells). G. An Epstein-Barr virus (EBV) in situ hybridization revealing EBV in the scattered atypical large cells (yellow arrows denote EBV-positive cells). H. Immunohistochemistry staining revealing large numbers of CD3-positive lymphocytes. I. Immunohistochemistry staining revealing large numbers of CD4-positive lymphocytes.
large atypical CD20-positive B-lymphocytes; angiitis due to transmural infiltration of the arteries and veins by lymphocytes; and granulomatosis (central necrosis within the lymphoid nodules in the absence of granuloma formation) (13). In situ hybridization often reveals EBV RNA within the atypical B-cells. The proportions of atypical large B-lymphocytes and, to a lesser degree, EBV-positive B-lymphocytes allow the clinician to classify the disease (grade 1-3) and make a prognosis (1). There is overlap between grades 2 and 3 with respect to the variants of large B-cell lymphoma, and many of these cases show evidence of monoclonality during polymerase chain reactions. It has been suggested that lymphoma (T-cell rich large B-cell or diffuse large B-cell) should be diagnosed in addition to LYG in grades 2 and 3, in order to appropriately communicate the nature of the disease to clinicians (2). In fact, LYG and other EBV associated lymphoproliferative diseases have similar causes, symptoms and therapies, and LYG is just a step away from lymphoma. Most importantly, an experienced pathologist is required for the definitive diagnosis of LYG.

The authors state that they have no Conflict of Interest (COI).

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