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

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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

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-

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gal) was subsequently adopted, but the patient's symptoms persisted. Empirical antibiotic therapy (including antifungal) was subsequently adopted, but the patient’s symptoms of fever, dry cough and dyspnea 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.

**Table. Laboratory Test Results on Admission.**

| Test item                        | Test value | Normal range   | Test item                        | Test value | Normal range   |
|----------------------------------|------------|----------------|----------------------------------|------------|----------------|
| White blood cell counts (10^9/L) | 4.31       | 3.5-9.5        | Complement 3 (g/L)               | 0.885      | 0.9-1.8        |
| Neutrophils percentage (%)       | 46.3       | 40-75          | Complement 4 (g/L)               | 0.208      | 0.1-0.4        |
| Lymphocyte percentage (%)        | 46.8       | 20-50          | Antinuclear antibody             | negative   | negative       |
| Hemoglobin (g/L)                 | 131.0      | 120-140        | Anti-double-stranded DNA antibody | negative   | negative       |
| Platelets (10^9/L)               | 63.0       | 125-350        | Rheumatoid factor                | negative   | negative       |
| Blood urea nitrogen (mmol/L)     | 4.69       | 2.29-7.0       | Antineutrophilic plasmid antibody | negative   | negative       |
| Creatinine (μmol/L)              | 77.5       | 53-106         | Anti-human immunodeficiency virus antibody | negative   | negative       |
| Alanine transaminase (U/L)       | 32.6       | 9-50           | Hepatitis C virus antibody        | negative   | negative       |
| Glutamic-oxal acetic transaminase (U/L) | 54.7   | 15-40          | Hepatitis B virus surface antigen | negative   | negative       |
| Total bilirubin (μmol/L)         | 14.0       | 5-20           | Plasma (1,3) beta-D-glucan (pg/mL) | 10.0       | <60            |
| Direct bilirubin (μmol/L)        | 3.3        | 1.7-10         | Serum galactomannan antigen       | negative   | negative       |
| Albumin (g/L)                    | 28.1       | 40-55          | Anti-EBV-EA immunoglobulin M antibody | negative   | negative       |
| Lactate dehydrogenase (U/L)      | 493.2      | 135-225        | Anti-EBV-VCA immunoglobulin M antibody | negative   | negative       |
| CD4 cell counts (cells /μL)      | 1,502.0    | 600-800        | Anti-CMV immunoglobulin M antibody | negative   | negative       |
| Erythrocyte sedimentation rate (mm/hr) | 3.0       | <15            | Anti-HPVB19 immunoglobulin M antibody | negative   | negative       |
| High-sensitivity C-reactive protein (mg/L) | 14.1     | 0-3            | Anti-HPV-B19 immunoglobulin G antibody | negative   | negative       |
| Procalcitonin (ng/mL)            | 0.07       | <1.0           | Anti-Mycoplasma immunoglobulin M antibody | negative   | negative       |
| Transferrin (g/L)                | 1.83       | 2.0-3.6        | Anti-Chlamydia immunoglobulin M antibody | negative   | negative       |
| Immunoglobulin A (g/L)           | 0.637      | 0.7-4.0        | CMV DNA (copies/mL)              | <500       | <500           |
| Immunoglobulin G (g/L)           | 4.92       | 7.0-16.0       | EBV DNA (copies/mL)              | 25,900     | <500           |
| Immunoglobulin M (g/L)           | 0.182      | 0.4-2.3        | EBV DNA (copies/mL)*             | 14,200     | <500           |

EBV: Epstein-Barr virus, CMV: cytomegalovirus, EA: early antigen, VCA: viral capsid antigen, HPV-B19: human parvovirus B19, “*”: EBV DNA value of 4 weeks later.
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 toxic 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.

Figure 1. Morphological presentation of pulmonary lymphomatoid granulomatosis. A. Hemophagocytosis 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.

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-
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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References

1. de Boysson H, Geffray L. Lymphomatoid granulomatosis. Rev Med Interne 34: 349-357, 2013 (in French, Abstract in English).
2. Katzstein AL, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol 34: e35-e48, 2010.
3. Pathak V, Aryal G, Clouse LH. Pulmonary lymphomatoid granulomatosis presenting with neuropathy and renal nodules. WMJ 111: 61-64; quiz 65, 2012.
4. Roschewski M, Wilson WH. Lymphomatoid granulomatosis. Cancer J 18: 469-474, 2012.
5. Dunleavy K, Roschewski M, Wilson WH. Lymphomatoid granulomatosis and other Epstein-Barr virus associated lymphoproliferative processes. Curr Hematol Malig Rep 7: 208-215, 2012.
6. Boone JM, Zhang D, Fan F. Lymphomatoid granulomatosis: a case report with unique clinical and histopathologic features. Ann Clin Lab Sci 43: 181-185, 2013.
7. Chung JH, Wu CC, Gilman MD, Palmer EL, Hasserjian RP,
Shepard JA. Lymphomatoid granulomatosis: CT and FDG-PET findings. Korean J Radiol 12: 671-678, 2011.

8. Ridene I, Radhouani I, Ayadi A, et al. Imaging features of primary pulmonary lymphomas. Rev Mal Respir 27: 1069-1076, 2010.

9. Braunlich J, Seyfarth HJ, Gessner C, Gradistanac T, Wirtz H. Lymphomatoid granulomatosis: a short description of an unusual case of the disease. Pneumologie 63: 697-701, 2009.

10. Gitelson E, Al-Saleem T, Smith MR. Review: lymphomatoid granulomatosis: challenges in diagnosis and treatment. Clin Adv Hematol Oncol 7: 68-70, 2009.

11. Ammannahari N, Srivali N, Price C, Ungprasert P, Leonardo J. Lymphomatoid granulomatosis masquerading as pneumonia. Ann Hematol 92: 981-983, 2013.

12. Olusina D, Ezemba N, Nzewwu MA. Pulmonary lymphomatoid granulomatosis: report of a case and review of literature. Niger Med J 52: 60-63, 2011.

13. Colby TV. Current histological diagnosis of lymphomatoid granulomatosis. Mod Pathol 25 (Suppl 1): S39-S42, 2012.