Clinical Case Report

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Rare case of pulmonary lymphomatoid granulomatosis in conjunction with tuberculosis

A case report

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Abstract

Rationale: Lymphomatoid granulomatosis is a very rare Epstein-Barr virus-driven lymphoproliferative disease. This disease has high mortality owing to its low incidence in conjunction with nonspecific presentations, which contribute to delays in diagnosis.

Patient: An 87-year-old male had a week-long history of intermittent fever and general weakness. A chest radiograph showed multifocal patchy consolidations with nodular lesions.

Diagnoses: Open lung biopsy using video-assisted thoracic surgery resulted in a diagnosis of grade III lymphomatoid granulomatosis. Three days after surgery, *Mycobacterium tuberculosis* complex was identified from the culture of sputum samples collected at admission.

Intervention and outcomes: Antituberculous treatment was commenced first. However, after 34 days of antituberculosis medication, the patient died owing to aggravated lymphomatoid granulomatosis.

Lessons: This case highlights the fact that rare diseases should also be considered in differential diagnosis, particularly with a common presentation such as multiple lung nodules. Furthermore, a diagnosis of pulmonary lymphomatoid granulomatosis was made after open lung biopsy. To our knowledge, this is the first case of lymphomatoid granulomatosis coexisting with active tuberculosis in the Republic of Korea, where tuberculosis is endemic.

Abbreviations: AFB = acid-fast bacilli, ANA = antinuclear antibodies, anti-HCV = antihepatitis C antibody, BAL = bronchoalveolar lavage, CRP = C-reactive protein, CT = computed tomography, EBER = Epstein-Barr virus-encoded small RNA, EBV = Epstein-Barr virus, ECOG = Eastern Cooperative Oncology Group, ESR = erythrocyte sedimentation rate, GMS = Grocott–Gomori's methenamine silver, HBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, hpf = high-power field, IFN-γ = interferon gamma, LDH = lactate dehydrogenase, LYG = lymphomatoid granulomatosis, PAS = periodic acid–Schiff, PCNB = percutaneous core needle biopsy, PLG = pulmonary lymphomatoid granulomatosis, Th1 = type 1 helper T lymphocyte, VATS = video-assisted thoracic surgery, WBC = white blood cell, WHO = World Health Organization.

Keywords: Epstein-Barr virus, pulmonary lymphomatoid granulomatosis, pulmonary tuberculosis

1. Introduction

Pulmonary lymphomatoid granulomatosis (PLG), which has been defined as a clinicopathological entity is a rare Epstein–Barr virus (EBV)-driven lymphoproliferative pulmonary disorder. It involves an angiocentric and angiodestructive process that affects the lung, via the invasion of bilateral nodular infiltrates composed of EBV-driven B-cells that lack true granulomatous features, and subsequent destruction of blood vessels.[1,2] Clinical manifestation suggestive of an atypical lymphoma and pulmonary vasculitis represents an overlap syndrome between angiitis and lymphoma. Thus, various pathogenetic conditions can be comprised in autoimmunity, infection, and malignancy.[3,4]

Lymphomatoid granulomatosis is usually observed as primary lesions in the lung; however, nonspecific clinical features of PLG are similar to those of more common pulmonary disorders, including tuberculosis, histoplasmosis, Wegener's granulomatosis, Churg-Strauss syndrome, sarcoidosis, cryptogenic organizing pneumonia, and malignancy.[5] Its low incidence combined with manifestations that overlap with other diseases results in difficulty diagnosing PLG. Other common sites of extranodal involvement include kidney (40%–50%), skin (25%–50%), central (25%–50%) or peripheral (15%–20%) nervous system, liver (10%), spleen (10%), and lymph nodes (<10%).[6]

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The case report was approved by the institutional review board of Korea University Anam Hospital (No. AN17098–001). Informed consent was obtained from the patient's son for publication of this case report and the associated images.

The authors declare no conflicts of interest.

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A complex relationship exists between lymphomatoid granulomatosis and functioning of the host's immune system.[6] Most patients have been diagnosed in conjunction with autoimmune diseases, chronic hepatitis infections, postorgan transplantation and postintensive therapy for malignancy.[7–9] Treatment options of these patients includes corticosteroids, anti-CD20 monoclonal antibodies, interferon-α-2b and combination chemotherapy, but PLG has extremely poor prognosis.

Herein, we report a case of PLG in conjunction with active tuberculosis. To our knowledge, this manifestation has not been previously described.

2. Case report

The patient was an 87-year-old male, nonsmoker, with a known history of pulmonary tuberculosis 14 years previously and complete recovery from prostate cancer 10 years earlier, who was also diagnosed with type 2 diabetes mellitus, hypertension, and hypothyroidism. Previous diagnosis of pulmonary tuberculosis was confirmed based on a positive culture for *Mycobacterium tuberculosis*. He was treated with a standard four-drug therapy for drug-susceptible tuberculosis. However, a negative sputum culture for *M. tuberculosis* was not confirmed during the 6-month treatment, owing to improvement of his respiratory symptoms. After recovery, the patient was subsequently rehospitalized for treatment of prostate cancer. Although the patient lived in South Korea, which has a high prevalence of tuberculosis, he did not report of any memorable exposure to patients with active tuberculosis.

He was regularly taking the following medications: metformin and saxagliptin for diabetes, levothyroxine sodium hydrate for hypothyroidism, and ramipril for hypertension.

The patient presented to our hospital with a week-long history of intermittent fever and general weakness. On admission, he had a cough, poor oral intake, and experienced dyspnea after walking for a few minutes on level ground. General physical examination revealed bilateral crackles and rales on both lung fields. There was no evidence of cardiac murmur, lymphadenopathy, hepatosplenomegaly, or skin lesion. No Osler nodes, Janeway lesions or splinter hemorrhages were observed.

In the initial laboratory results, the patient's complete blood counts were as follows: hemoglobin 9.9 g/dL (normal limits 12~16 g/dL), white blood cell (WBC) count 9500/μL (normal limits 4,500~11,000/μL), and platelet count 376,000/μL (normal limits 150,000~400,000/μL). WBC differential count with neutrophilia was 7837/μL (82.5%, normal limits 45%~75%). Erythrocyte sedimentation rate (ESR) of 57 mm/hr (normal limits 0~20 mm/hr) and C-reactive protein (CRP) of 57.4 mg/L (normal limits 0~5 mg/L) were mildly elevated; procalcitonin was 0.14 ng/mL (normal limits 0~ 0.05 ng/mL). A chest radiograph and computed tomography (CT) scan showed multifocal patchy consolidations with nodular lesions of variable sizes and irregular margins combined with right pleural effusion, but there was no hilar or mediastinal lymphadenopathy (Fig. 1 A and B).

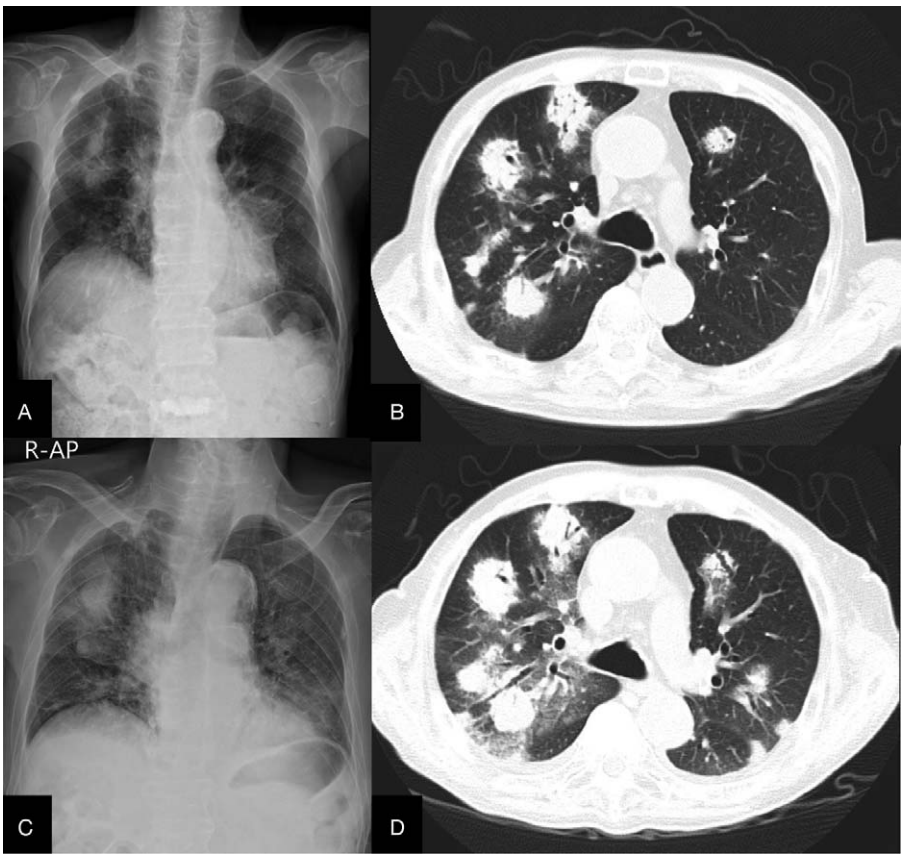

Figure 1. (A) Initial chest radiograph showing multiple nodular lesions in both lung fields. (B) Chest computed tomography (CT) scans revealing multifocal consolidations with ground-glass opacity and right pleural effusion. (C and D) Follow-up chest radiograph and chest CT scans demonstrating interval aggravation of multiple nodular opacities.

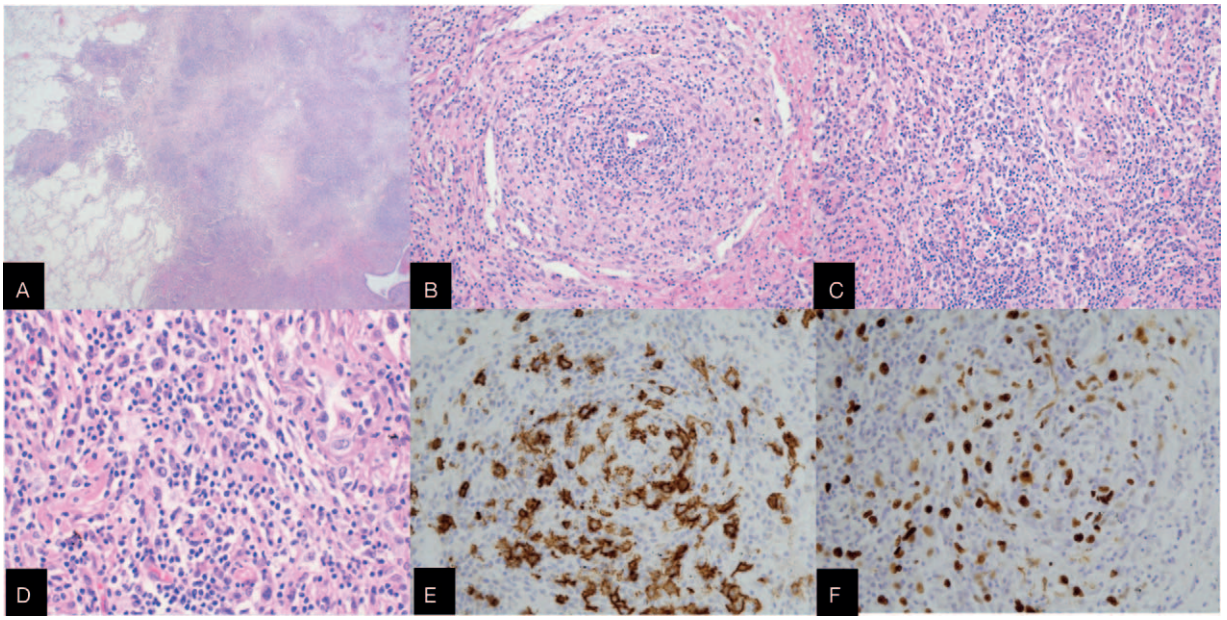

Figure 2. A, A well-circumscribed mass destroying lung parenchyma, composed of proliferated lymphoid cells (H & E stain, × 40). B, Histologic appearance shows transmural infiltration of atypical lymphoid cells around small- and medium-sized vessel walls (H & E stain, × 200). C, Most infiltrated cells are scattered, large atypical lymphoid cells with small lymphocytes, plasma cells, and histiocytes (H & E stain, × 200). D, Some atypical lymphoid cells are binucleated, similar to Reed–Sternberg cells (H & E stain, × 400). E, Immunohistochemical staining shows scattered CD20-positive large atypical B cells (H & E stain, × 400). F, These large B cells are positive for EBV by in situ hybridization (H & E stain, × 400).

Early differential diagnosis of fever and lung nodules included tuberculosis, pulmonary septic emboli, fungal infection, vasculitis, and malignancy. Transthoracic echocardiography demonstrated no evidence of infective endocarditis. Analysis of pleural effusion showed a WBC count of 340/mm^3 with 94% lymphocytes, 4% neutrophils, and 2% monocytes, protein of 1.9 g/dL, lactate dehydrogenase (LDH) of 231 U/L, and pH of 8.0. Polymerase chain reaction for *M. tuberculosis* and cytology for malignancy were all negative. Fiber optic bronchoscopy with bronchoalveolar lavage (BAL) was inconclusive. All blood culture using the BacT/ALERT 3D Microbial Detection System (bioMérieux, Inc., Durham, NC) and sputum cultures using Vancomycin-Bacitracin-Clindamycin agar, MacConkey agar, and blood agar plates were negative for bacterial or fungal growth. Respiratory specimens, including BAL fluid, taken for acid fast bacillus (AFB) staining on more than three occasions were negative. A viral work-up for hepatitis B surface antigen (HBsAg), antihepatitis C antibody (anti-HCV) and human immunodeficiency virus (HIV), respectively; an autoimmune disease work-up for antinuclear antibodies (ANA) and a fungal work-up for *Aspergillus* antigen were also negative.

Under the clinical diagnosis of bacterial pneumonia, cefepime (2 g, twice daily) and intravenous teicoplanin (400 mg, once daily) were administered as empirical antibiotic therapy. However, after 2 weeks of antimicrobial treatment, follow-up chest radiograph and chest CT scans showed numerous aggravated nodular densities with cavities (Fig. 1 C and D), and his Eastern Cooperative Oncology Group (ECOG) scale of performance status deteriorated from grade II to grade IV. Thus, amphotericin B deoxycholate was prescribed concurrently based on a suspicion for fungal pneumonia.

Percutaneous core needle biopsy (PCNB) of the left lung was performed to differentiate between the suspected diagnoses of fungal pneumonia and malignancy. However, histological examination revealed only nonspecific findings of interstitial chronic inflammation with fibrosis and focal necrosis. After maintaining the combination antimicrobial therapy for 28 days, multifocal patchy consolidations with nodular lesions on chest CT scan showed no further improvement. Accordingly, open lung biopsy using video-assisted thoracic surgery (VATS) was conducted for wedge resection of the right lung (middle and lower lobes). The histopathology showed grade III lymphomatoid granulomatosis, composed of polymorphous infiltrate with large atypical and small lymphoid cells showing angiocentricity with fibroblastic stroma (Fig. 2).

The large atypical cells and small lymphocytes were positive for CD20 and CD3, respectively. The atypical lymphoid cells were positive for Epstein-Barr virus-encoded small RNA (EBER) with > 50/high-power field (hpf). Grocott–Gomori's methenamine silver (GMS) and periodic acid–Schiff (PAS) stains revealed no fungal organisms. The AFB stain was negative and there was no granulomatous lesion consistent with mycobacterial infection on our biopsy specimen.

On the 30th day of hospitalization, a therapeutic plan for PLG was carefully established with intensive CHOP and rituximab; however, the initiation of chemotherapy was delayed because of general weakness of the patient. Subsequently, *M. tuberculosis* complex, which is susceptible to all antituberculous drugs, was identified on the 36th day of hospitalization from the culture of sputum samples collected at admission. Therefore, anticancer treatment was deferred until after antituberculous treatment. After 34 days of antituberculosis medication, the patient showed a consciousness deterioration and became completely disabled. The patient's subsequent death was attributed to have resulted because of the disease progression of PLG.

3. Discussion

PLG is a rare disease entity in the differential diagnosis of multiple pulmonary nodules. The rareness of PLG together with its

nonspecific clinical manifestations and radiological findings make its diagnosis difficult. PLG is even harder to cure because of the lack of an established treatment strategy. In our patient, the presentation of confounding features that were suggestive of pulmonary septic emboli, fungal pneumonia or lung abscess, and no prominent aggravation of pulmonary nodules during antimicrobial therapy for Gram-positive and Gram-negative germs, together contributed to delay in diagnosis.

The definite diagnosis of PLG hinges on histopathology, with mixed mononuclear cell infiltrate containing several CD20-positive large B-cells in a background of CD3-positive small lymphocytes. These findings are often accompanied by plasma cells and histiocytes, which together replace the lung parenchyma and cause vascular infiltration, as in our case. Multiple lung nodules radiologically with necrosis of the cellular infiltrate and positive EBER in situ hybridization were useful supportive findings. However, there was no skin or nervous system involvement, defined as optional manifestations.

As shown in our case, although the lung is the primary site of involvement, sputum cytology, transthoracic needle aspiration, and PCNB did not support PLG diagnosis. To obtain adequately sized lung tissue samples for evaluation, VATS or open thoracotomy should be performed at an early stage of diagnosis. Similar to our case, several previously reported cases of PLG were confirmed by open lung biopsy because transbronchial or percutaneous needle biopsy were inconclusive.[10–12]

PLG with diverse synonyms including angiocentric immunoproliferative lesion and angiocentric lymphoma, is currently classified as part of a spectrum of angiocentric and immunoproliferative lesions, composed of lymphoreticular cells lacking true granulomatous features.[13] This case was initially thought to be of T-cell phenotype, but recent papers have shown that PLG is an EBV-positive B-cell proliferation associated with an exuberant T-cell response.[1,14] This unusual disease is adversely affected by the uncommon complication of intercurrent tuberculosis.[15,16] The type 1 helper T lymphocyte (Th1) response, capable of synthesizing interferon gamma (IFN-γ) and other cytokines, contains *M. tuberculosis* in a latent state without active replication. Alteration of the Th1 cell response in PLG might lead to an impaired immune response that most likely promotes the progression from latent tuberculosis infection to its active form.[17]

PLG complicated with tuberculosis is an extremely rare and challenging condition owing to confusion in differential diagnosis, and it is usually incompatible with treatment for both diseases. In this case, commencing immune-suppressing chemotherapy in a much debilitated patient could aggravate the clinical severity of primary infections and the risk of drug toxicity. Thus, we had no choice but to defer chemotherapy and start antituberculosis therapy alone.

To prioritize risks and justify the treatment strategy, a formal staging system for the diagnosis of PLG would be valuable. The World Health Organization (WHO) recommends that lymphomatoid granulomatosis (LYG) be classified as grade I, grade II, or grade III, according to the number of EBV-positive large B-cells. Grade 1 is a finding of < 5 EBV-positive cells per hpf, and grade 3 is > 50 EBV-positive cells per hpf. However, there is considerable variation in EBV-positive cell counts between specimens.[13] Therefore, the treatment strategy is generally established comprehensively, based on the presence and severity of symptoms, the extent of extrapulmonary involvement, the histopathologic grade of the lesion and underlying diseases. Our case was categorized as grade 3, according to the WHO grading system, which corresponds to high-grade PLG

Options in the management of patients with lower-grade PLG includes treating the cause of immune dysfunction and observation for regression. Patients with higher-grade PLG require immediate therapy similar to aggressive lymphoma, including corticosteroids, anti-CD20 monoclonal antibodies, interferon α-2b, anticancer chemotherapy, radiotherapy and hematopoietic stem cell transplantation.[7,13] However, no standard treatment has yet been established. The disease is aggressive in most patients, with median survival of 2 years; the 5-year mortality is 60% to 90%.[18] Additional clinical data for development of a formal staging system and therapeutic plan for PLG should be collected, to improve the prognosis.

In conclusion, though uncommon, the possibility of PLG should be considered with a high degree of suspicion in differential diagnosis of lung nodules. In addition, if PLG is suspected, invasive investigations such as open lung biopsy should be performed, to reach an early diagnosis. Another implication of this report is that in patients from countries with high incidence of tuberculosis, it should be determined whether PLG is accompanied by tuberculosis.

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