Lymphoid Interstitial Pneumonia Associated with Common Variable Immunoglobulin Deficiency

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Abstract

The patient was a 30-year-old woman with a disease of common variable immunodeficiency. She was admitted to our hospital because of abnormal findings on her chest radiographs in an annual health screening. Chest computed tomography showed multiple reticulonodular infiltrates in both lower lung fields. The surgical lung biopsy specimen demonstrated involvement of mature small lymphocytes with a mixture of other mononuclear cells in the lung parenchyma and bronchiolar walls. The patient was diagnosed to have lymphoid interstitial pneumonia. The patient was treated with prednisolone and intravenous supplement of immunoglobulin, resulting in radiographically and clinically stable disease.

Key words: hypogammaglobulinemia, interstitial pneumonia, thoracoscopic lung biopsy

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Introduction

Lymphoid interstitial pneumonia (LIP) is a rare clinicopathological entity. The microscopic feature is characterized by diffuse infiltration of polyclonal lymphoid cells surrounding airways and expanding the lung interstitium (1-3). LIP has been thought to be within the spectrum of pulmonary lymphoproliferative disorders (4). LIP is typically associated with a number of diverse systemic diseases such as Sjogren’s syndrome, autoimmune thyroid disease, human immunodeficiency virus infection and various immunodeficiency states including common variable immunodeficiency (CVID) (1-10). LIP associated with CVID was initially reported by Liebow and Carrington in 1973 (1). The clinical course is variable; some patients successfully respond to corticosteroid therapy, other show progressive pulmonary fibrosis resulting in a fatal outcome within a short time (5, 8-10). In addition, the presence of LIP in patients with CVID was associated with a worse prognosis compared to those without pulmonary complications (7).

Here, we report a case of LIP associated with CVID who was treated with corticosteroid therapy combined with intravenous supplement of immunoglobulin. The patient has been stable both radiographically and clinically after the combination therapy.

Case Report

A 30-year-old woman visited our hospital for further evaluation of abnormal opacities on chest radiography detected by an annual health screening in November 2000. She was diagnosed as having CVID 2 years earlier because her laboratory findings included hypogammaglobulinemia. Although the patient had suffered from several episodes of sinusitis, there was no history of lower respiratory infections or symptoms. She had never smoked. On admission, there were no abnormal findings on physical examination. Hematological and biochemical analysis demonstrated the following: erythrocyte sedimentation rate, 1 mm/hour; white blood cells, 3,410/µl; hemoglobin, 14.5 g/dl; platelets, 11.6×10³/µl; total protein, 6.6 g/dl; albumin, 4.8 g/dl (73.2%); gammaglobulin α₁, 0.19 g/dl (2.9%); α₂, 0.61 g/dl (9.3%); β, 0.77 g/dl (11.6%); γ, 0.2 g/dl (3.0%); immunoglobulin (Ig) A, 6 mg/dl; IgM, 23 mg/dl; IgG, 184 mg/dl; IgD, 0.7 mg/dl; IgE, 2 IU/ml; KL-6, 686 U/ml and serum C-reactive protein,
Figure 1. Chest radiography (A) and chest computed tomography (B) on the initial hospitalization demonstrated reticular and multiple node shadows on both lung fields.

Figure 2. A: The biopsy specimens showed lymphoid cells diffusely involving the lung parenchyma of alveolar septa, interlobular connective tissue (Hematoxylin and Eosin staining ×40). B and C: Immunohistochemical study revealed that the involved cells were positive for T (CD3, Fig. 2B) and B (CD20, Fig. 2C): lymphocyte antibody, respectively (×100).

0.10 mg/dl. She was negative for human immunodeficiency virus. Arterial blood gas analysis in room air showed PaO₂ of 95.9 mmHg, PaCO₂ of 36.3 mmHg, and pH of 7.42. Pulmonary function tests were within the normal range, including diffusion capacity. Chest radiography and CT scans demonstrated multiple nodules along lymphatic vessels predominantly in both lower lung fields (Fig. 1A, 1B). Splenomegaly was also observed on abdominal CT examination. Analysis of bronchoalveolar lavage fluid (BALF) were total cells of $10.9 \times 10^5/\mu l$ with differential counts of alveolar macrophage (29.0%), lymphocytes (67.4%), neutrophils (1.0%) and eosinophils (2.6%), and a CD 4/8 ratio of 2.9. Video-assisted thoracoscopic lung biopsy was performed from right segment 4 and segment 8. The biopsy specimens showed lymphoid cells diffusely involving lung parenchyma of the alveolar septa, interlobular connective tissue (Fig. 2A). Germinal centers and granulomatous lesions with a few giant cells were observed. Lymphoid cells, which in-
Figure 3. Chest radiography (A) and chest computed tomography (B) on the second hospitalization (Aug. 2004) demonstrated reticular and multiple node shadows on both lung fields.

Figure 4. Chest radiographic findings (December 2004) were improved 3 months after corticosteroid and immunoglobulin replacement therapy.

filtrated in the fibrous interstitium, were a mixture of T cells (CD3-positive, Fig. 2B), B cells (CD20-positive, Fig. 2C), histiocytes (CD68-positive) and dendritic cells (S100-positive). T cells were slightly more predominant than B cells, and B cells were often observed in the germ centers. Lymphoid cells were markedly aggregated in the bronchiolar walls, and these lesions looked like small nodules. Normal lung alveoli intervened these parenchyma involved by small lymphoid cells and other mononuclear cells. In some regions, the small lymphoid cells showed an expanding growth pattern. Based on these pathological findings, diagnosis of LIP was made.

She was initially treated with prednisolone 30 mg/day. Radiographic findings showed an improvement on her chest radiograph, however, she discontinued medication and had not returned to the clinic for approximately one year. The patient was readmitted to our hospital because of acute abdomen in August 2004. She underwent an abdominal operation based on the diagnosis of acute peritonitis due to appendicitis. At the time, chest radiograph and CT showed almost similar findings as those of the initial diagnosis of LIP (Fig. 3A, 3B). After recovery of the surgery and infection, she has been treated with 20 mg/day of prednisolone combined with intravenous supplement of immunoglobulin (5 g/day) given at 2-week intervals. After that, there are no infectious events and Ig G levels have ranged from 390 to 470 mg/dl. Serial chest radiographic findings following the therapy are shown in Figs. 4, 5. The radiographic findings improved (Fig. 4) and have been stable (Fig. 5) for 3 years after the combination therapy. Thus, combined therapy of corticosteroid and immunoglobulin supplement seems to stabilize pulmonary involvement of LIP associated with CVID.

Discussion

We report a case of LIP associated with CVID. It is reported that 60-80% of the patients with LIP have evidence of dysproteinemia (4) in which the most frequent case was
Figure 5. Chest radiographic findings in October 2007 were stable during corticosteroid and immunoglobulin replacement therapy for 3 years.

polyclonal hypergammaglobulinemias due to an elevation of various types of immunoglobulin (4, 5). Hypogammaglobulinemia including CVID associated with LIP is less but has been documented for 20 years (1). Recently, Bates et al (7) summarized noninfectious pulmonary complications in patients with CVID, which were confirmed by surgical lung biopsies. Although several histological patterns including granulomatous and lymphoproliferative diseases and/or both overlapping were present, the overall prevalence was 26% of patients with CVID. In addition, they described that 10% of CVID patients had LIP, lymphoid hyperplasia, or follicular bronchiolitis. Thus, LIP seems to be common in patients with CVID.

Histologically, the overlap or coexistence of granulomatous and lymphoproliferative lesions has been identified in LIP (5, 7). However, the presence of granulomatous and/or lymphoproliferative pulmonary diseases in patients with CVID was associated with a worse prognosis compared to those with and without other pulmonary complications (7). In addition, splenomegaly was also an important risk factor in patients with CVID (7, 9), which was observed in the present case.

The optimal treatment for LIP is not well established because of the small number of patients. Most cases have been treated with long-term corticosteroids, but other immunosuppressive agents are also suggested (6). However, it is unlikely that prolonged use of these agents is suitable for patients with CVID. In the present case, radiographic findings were improved and kept stable after a small dose of corticosteroid and immunoglobulin replacement therapy. It is speculated that intravenous immunoglobulin therapy synergically contributed to further control pulmonary diseases in the present case as well as to prevent infections (11). However, Davies et al (6) reported a case of CVID, bronchiectasis and autoimmune hemolytic anemia who developed LIP after intravenous immunoglobulin replacement therapy. Thus, the standard therapy for LIP in patients with CVID remains to be elucidated.

Immunopathologic studies of LIP in non-AIDS patients demonstrate abundant L-26 (CD20)-positive B cells, particularly within peribronchial lymphoid aggregates (2). On the contrary, a few reports in LIP associated with hypogammaglobulinemia suggested that histological findings are characterized by infiltration of the alveolar interstitium by T lymphocytes (4, 5). In the present case, immunohistological examination showed a mixture of T and B lymphocytes in the lung interstitium, although T cells were slightly predominant compared with B cells. The clinical meaning in the different lymphocyte distribution in patients with LIP remains unknown. It is necessary to evaluate a clinical and pathological correlation of the aggregation of lymphoid cells in patients with LIP. In addition, more than 30% of LIP progresses to malignant lymphoma (10-13), especially in patients with CVID or in those with monoclonal gammopathy. Radiographic features of LIP were indistinguishable from findings of the neoplastic cellular proliferation (7, 13). We think that lung biopsy by VATS is required to establish the correct diagnosis for progressive lung diseases and for further pathological examination of LIP.

In summary, we reported a case of LIP accompanied with CVID. The patient was treated with a low dose of corticosteroid and immunoglobulin replacement therapy for 3 years. Radiological findings were improved and kept stable, as well as the prevention for infection. Noninfectious pulmonary complications in patients with CVID may be common and surgical lung biopsy should be considered for definitive histological diagnosis, especially in patients with CVID who exhibit diffuse lung disease.

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