Intravenous Immunoglobulin Monotherapy for Granulomatous Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency

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Abstract:
Common variable immunodeficiency (CVID) is a heterogeneous subset of immunodeficiency disorders. Recurrent bacterial infection is the main feature of CVID, but various non-infectious complications can occur. A 42-year-old woman presented with cough and abnormal chest X-ray shadows. Laboratory tests showed remarkable hypogammaglobulinemia. Computed tomography revealed multiple consolidation and nodules on the bilateral lung fields, systemic lymphadenopathy, and splenomegaly. A surgical lung biopsy specimen provided the final diagnosis of lymphoproliferative disease in CVID, which was grouped under the term granulomatous lymphocytic interstitial lung disease. Interestingly, the lung lesions of this case resolved immediately after the initiation of intravenous immunoglobulin monotherapy.

Key words: granulomatous lymphocytic interstitial lung disease, common variable immunodeficiency, lymphoproliferative disease, hypogammaglobulinemia, intravenous immunoglobulin therapy

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Introduction

Common variable immunodeficiency (CVID) is a heterogeneous subset of immunodeficiency disorders of unknown etiology that leads to hypogammaglobulinemia with marked reduction of immunoglobulin (Ig)G and IgA and a variable decrease in IgM. It is caused by a disorder of B-cell differentiation, resulting in a decrease in the numbers of memory B-cells and plasma cells and the inability to produce specific antibodies. Patients with CVID frequently have low numbers of CD4+ T-cells (1-4). Recurrent bacterial infection is the main feature of CVID, but various non-infectious complications, such as malignancies, autoimmune diseases, and lymphoproliferative diseases, have been reported to occur (4, 5).

Granulomatous lymphocytic interstitial lung disease (GLILD) is a non-infectious, diffuse lung disease that occurs in CVID patients and presents with both granulomatous and lymphoproliferative histopathologic findings, such as lymphocytic interstitial pneumonia (LIP), follicular bronchitis, and lymphoid hyperplasia (6). GLILD has been reported to develop in approximately 10-20% of CVID patients, but its pathogenesis has not been fully elucidated. Several studies have suggested that CVID with GLILD is associated with increased mortality (7, 8). Various drug mono- or combination therapies with corticosteroids, immunosuppressive agents, infliximab, and rituximab, have been used for GLILD (9, 10).
We herein report a case of GLILD as an early manifestation of CVID in a patient whose pulmonary lesion immediately improved after the initiation of intravenous immunoglobulin (IVIg) therapy. Since most of the reported cases of GLILD did not improve after the initiation of IVIg therapy alone, our case was rare and may be of interest in understanding the pathogenesis of GLILD in CVID.

Case Report

A 42-year-old Japanese woman was referred to our institution after she presented with a cough for 1 month and abnormal shadows on chest X-ray. She was a never-smoker. She had medical histories of anemia from the age of 20 years and atrichia in her early teenage years. On a physical examination, wheezing was heard in both lungs. Laboratory tests showed marked hypogammaglobulinemia, anemia, and elevation of serum soluble interleukin (sIL)-2 receptor; other values were hemoglobin 8.5 g/dL, IgG 409 mg/dL, IgA 39 mg/dL, IgM 27 mg/dL, and sIL-2 receptor 1,260 U/mL. The serum levels of angiotensin-converting enzyme and lysozyme were within the normal range. The CD4+ T-cell count was within the normal range at 518/μL. Serum antibodies to Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), and human herpes virus type 8 (HHV-8) were negative. Likewise, antibodies suggesting autoimmune disease were all negative.

Chest X-ray revealed patchy consolidation and ill-defined nodules with lower lung field predominance. Chest and abdominal computed tomography (CT) revealed multiple patchy consolidations and ill-defined nodules along the perilymphatic interstitium, with lower lobe predominance, thickening of the bronchovascular bundle and interlobular septa, systemic lymphadenopathy, and splenomegaly (Fig. 1). A bronchoalveolar lavage fluid analysis revealed elevation of lymphocytes; the total cell count was 2×10⁵/mL, the proportion of lymphocytes was 25.5%, and the CD4/CD8 ratio was 1.9. Culture of the bronchoalveolar lavage fluid for mycobacteria, bacteria, and fungi were all negative.

Video-assisted thoracoscopic surgery was performed for a biopsy of the right upper and lower lobes of the lung. A macroscopic examination of the lung specimen revealed multiple white nodules along the perilymphatic structures, and a microscopic examination revealed lymphocyte infiltration and lymphoid hyperplasia along the bronchus, bronchiole, and vessels, without lymphoepithelial lesions (Fig. 2).
The absence of CD20+ and CD3+ cell monoclonality on immunohistochemical staining and a negative IgH-BCL2 translocation on a genomic analysis ruled out malignant lymphoma. A small number of non-caseous epithelioid cell granuloma was observed. Ziehl-Neelsen staining, Grocott staining, and EBV-encoded small RNA (EBER) in situ hybridization were negative. The pathologic diagnosis was lymphoproliferative disease (LPD) of the lung. A surgical biopsy of an inguinal lymph node also revealed polyclonal lymphocyte infiltration and lymphoid hyperplasia without evidence of malignancy.

The hematologist clinically diagnosed her with CVID, and the final diagnosis was LPD of the lung occurring in CVID, which is grouped under the term GLILD. Right-sided empyema and worsening of the lung lesions developed after VATS, but both improved immediately after the initiation of IVIg therapy. After 18 months of continuing IVIg therapy, the patient remained stable without recurrence of lung LPD and infectious diseases. However, the systemic lymphadenopathy and splenomegaly persisted, albeit improved to some extent.

**Discussion**

LPD in a patient with CVID is classified by the World Health Organization into one entity called immunodeficiency-associated LPD (11), which includes other immune disorders, such as HIV infection (HIV-LPD), post-transplant lymphoproliferative diseases (PTLD), and iatrogenic immunodeficiency, such as methotrexate-associated LPD (MTX-LPD). Granulomatous and lymphoproliferative histologic patterns, such as LIP, follicular bronchiolitis, and lymphoid hyperplasia, occurring in CVID have recently been grouped together under the term GLILD (6). GLILD develops in approximately 10-20% of CVID patients, but its pathogenesis has not yet been fully elucidated. Reactivation of EBV was suggested to be associated with the pathogenesis of HIV-LPD, MTX-LPD, and PTLD (12-14). Viruses, such as EBV, HIV, and HHV-8, were also suggested to play a role in the pathogenesis of LPD in CVID (6). However, in this case, *in situ* hybridization of the lung specimen was negative for EBER; serum antibodies to EBV, HIV, and HHV-8 were all negative; and the CD4+ T-cell count was within the normal range. Therefore, the pathogenesis of LPD in our case was unclear. Our case presented with
GLILD but had no episodes of recurrent bacterial infection, making it difficult to consider immunodeficiency as the underlying disease. It is important to note that immunodeficiency itself may cause LPD; therefore, screening of serum Ig levels is essential in patients with manifestations of LPD.

The lung lesions of our case improved immediately after the initiation of IVIg therapy. Previous studies have reported difficulties in treating GLILD with IVIg monotherapy or even with combination therapy with corticosteroids; in addition, there are no currently established guidelines for treatment (6, 15, 16). Since GLILD is an aggregation of various types of pulmonary granulomatous and lymphoproliferative disorders, including granulomatous disease, LIP, lymphoid hyperplasia, follicular bronchiolitis, and even B cell lymphoma (8), the evaluation and consolidation of therapeutic modalities seem difficult. Since the presence of granulomas can promote tissue damage and decrease the lung function, the quantity of granuloma may be associated with the prognosis of GLILD. This might explain the favorable response of our patient to IVIg monotherapy, since the pathologic findings showed a minimal amount of granuloma and mainly comprised follicular hyperplasia without a marked distortion of the parenchymal structures. In addition, our case did not present with lymphoepithelial lesions or monoclonality, ruling out a neoplastic process. The response to treatment might differ by histopathologic pattern and amount of granuloma, but further study is required to confirm this hypothesis.

In conclusion, immunodeficiency can cause LPD, and screening for Ig is essential in patients with LPD. Interestingly, the lung lesions in our case improved immediately after the initiation of IVIg. We assumed that the treatment response of GLILD varies according to the histologic type and amount of granuloma.

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

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