IgG4-related Lung Disease with Organizing Pneumonia Effectively Treated with Azathioprine

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Abstract

Immunoglobulin (Ig)-G4-related disease is a multi-organ disease that may affect the lung. We herein describe a patient with IgG4-related lung disease (IgG4-RLD) who was radiologically and pathologically diagnosed with organizing pneumonia. He was successfully treated with a combination of prednisolone (PSL) and azathioprine (AZA), and his clinical course has been uneventful since tapering off PSL. This is a rare case of IgG4-RLD manifesting as organizing pneumonia, and, to our knowledge, this is also the first case showing the effectiveness of AZA in treating IgG4-RLD.

Key words: IgG4-related lung disease, IgG4-related pulmonary disease, IgG4-related disease, organizing pneumonia, azathioprine, prednisolone

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Introduction

Since the first report on autoimmune pancreatitis (AIP) in 2001, IgG4-related disease (IgG4-RD) has been recognized as a form of systemic sclerosing disease (1). Pulmonary manifestations of IgG4-RD include inflammatory pseudotumor and interstitial pneumonia, but other lung manifestations may also occur (2). We herein describe a patient with IgG4-related lung disease (IgG4-RLD) presenting with organizing pneumonia. This patient relapsed during prednisolone (PSL) monotherapy but was effectively treated with a combination of PSL plus azathioprine (AZA).

Case Report

A 68-year-old man was referred to our department in April 2007 with swelling of the mediastinal lymph nodes, a thin tumor around the thoracic vertebrae, and an elevated serum IgG concentration (4,730 mg/dL). His previous medical history included a diagnosis of diabetes at age 63 years, and diagnoses of hyperuricemia, atrial fibrillation, and dilated cardiomyopathy at age 68 years. The examination of a lymph node biopsy taken under mediastinoscopy showed

only non-specific granulomatous changes, and no definite diagnosis was reached. Although the patient was not treated, the mediastinal lymph nodes decreased in size and his serum IgG level was reduced. In 2011, however, he began to feel dyspnea on exertion. A chest computed tomography (CT) revealed an infiltrative shadow with an air bronchogram in the lower lobes of both lungs (Fig. 1), and his serum IgG and IgG4 concentrations were again elevated. He was therefore admitted to our hospital. The patient was in good physical condition upon admission, with no evidence of crackles or heart murmur. The oxygen saturation was 97% (room air). The results of the respiratory function test were normal, with a vital capacity (VC) of 3.02 L (92.6% predicted) and a forced expiratory volume in one second (FEV1) of 2.32 L (98.3% predicted). His serum IgG (3,215 mg/dL; normal range 870-1,700 mg/dL) and IgG4 (1,260 mg/dL; normal range <105 mg/dL) concentrations were markedly elevated. His serum IgA (182 mg/dL) and IgM (69 mg/dL) concentrations were in the normal range. We also observed elevated serum concentrations of soluble interleukin (IL)-2 receptor (1,292 U/mL; normal range <519 U/mL), Krebs von den Lungen-6 (KL-6) (591 U/mL; normal range <500 U/mL), brain natriuretic peptide (BNP) (156 pg/mL; normal range <18.4 pg/mL), hemoglobin (Hb) A1c

Figure 1. (A) The chest X-ray upon admission showed widening of the right hilum, consolidation in the left lung field and cardiomegaly. (B, C) The chest CT showed swelling of mediastinal and right hilar lymph nodes. (D) The chest CT revealed a posterior mediastinal thin tumor around the thoracic vertebrae. (E, F) High-resolution CT revealed consolidation with air bronchogram in both lower lobes, and thickening of bronchial vascular bundles and interlobular septa in both the middle and lower lobes.

(6.5%; normal <5.9%), and IL-6 (6.9 pg/mL; normal <4.0 pg/mL), although his serum angiotensin-converting enzyme (ACE) (15.8 U/L) was in the normal range (8.3-21.4 U/L). He was negative for a variety of autoimmune antibodies, including anti-nuclear and anti-cyclic citrullinated peptide (CCP) antibodies. A chest X-ray (Fig. 1A) showed widening of the right hilum, infiltrative shadows in the lower field of the left lung and cardiomegaly. Chest CT revealed consolidation with air bronchogram in the right lower lobe S⁶ and left lower lobe, thickening of bronchial vascular bundles and interlobular septa in both the middle and lower lobes, mediastinal lymph node swelling, and a posterior mediastinal thin tumor around the thoracic vertebrae (Fig. 1).

The collection rate of bronchoalveolar lavage fluid at the right S⁸ bronchus was 40%, with a total cell count of 1.9×10^5 /mL and almost normal cell fractions: 86% macrophages, 9% lymphocytes, and 2% eosinophils, and a CD4/CD8 ratio of 1.4. Video-assisted thoracoscopic segmentectomy of the right S⁶ was performed, and pathologically ill-defined patchy lesions were observed at a low power field (Fig. 2). These patchy lesions consisted of organization in the airway cavity, lymphocytic infiltrates, plasma cells and a few eosinophils around alveolar septal walls and small blood vessels, and luminal exudates in the alveolar space. Immunostaining showed an increase in IgG-positive cells, with an IgG4/IgG ratio exceeding 60%, and no monoclonality in the light chain. The polymerase chain reaction (PCR) analysis revealed no monoclonal rearrangement in the immunoglobulin

heavy chain gene or T-cell receptor γ -chain gene.

These findings suggested a diagnosis of IgG4-RLD. The patient was treated with PSL (30 mg/day), which improved his dyspnea on exertion, chest CT findings, and IgG and IgG4 concentrations (Fig. 3). PSL was tapered, but eight months later, while the patient was receiving PSL (5 mg/day), multiple infiltrative shadows appeared in both lungs. Increasing PSL was temporarily effective, and a dose of 10 mg/day was inadequate. Treatment with PSL (20 mg/day) plus methotrexate (MTX) 5 mg/week was also ineffective. The patient was therefore treated with a combination of PSL (20 mg/day) plus AZA (50 mg/day), and marked improvement was observed within several weeks (Fig. 3). His clinical course thereafter has been uneventful, even after tapering off PSL.

Discussion

IgG4-RD is a disease involving multiple organs and includes AIP. Several patients with IgG4-RD were found to have interstitial pneumonia or other pulmonary lesions (3). Pulmonary parenchymal lesions of IgG4-RLD have been classified as “nodules or masses” or as “interstitial lung disease” (2). The nodules or masses are thought to correspond in part to conventional inflammatory pseudotumors, whereas interstitial lung disease has been defined mainly as lymphoproliferative lesions involving the peribronchial interstitium or interlobular septum, but may also include nonspe-

Figure 2. Histopathological findings obtained by video-assisted thoracoscopic surgery at right S⁶. (A, B) Low magnification view shows infiltration of lymphocytes, plasma cells, and a few eosinophils along with bronchial vascular bundles and the interlobular septa. Intra-alveolar organization with the proliferation of plasma cells is observed. The alveolar spaces are filled with luminal exudate (Hematoxylin and Eosin staining. A, 1× B, 4×). (C) Immunohistochemistry staining demonstrated infiltration of the IgG4-positive plasma cells (20×).

Figure 3. The clinical course.

cific interstitial pneumonia (NSIP)-like or organizing pneumonia-like lesions (4). The radiologic and pathologic examinations suggested that our patient had IgG4-related organizing pneumonia. Because this patient lacked typical extrapulmonary lesions such as AIP, other than a tumor around the thoracic vertebrae, it was important to differentiate IgG4-related organizing pneumonia from other diseases that exhibit organizing pneumonia. Chronic eosinophilic pneumonia, bacterial pneumonia, and drug-induced pneumonia were unlikely based on the clinical course. Although Sjögren syndrome may mimic IgG4-RD, our patient did not fulfill the diagnostic criteria for Sjögren syndrome. In addition, he did not have rheumatoid arthritis, which is occasionally associated with organizing pneumonia. Multicentric Castleman's disease (MCD) partially overlaps IgG4-RD, and differentiation between the two is sometimes difficult (5). MCD, however, often exhibits abnormal findings associated with in-

flammation, such as elevated C-reactive protein (CRP), hypoalbuminemia, anemia, and hypocholesterolemia (6). Based on the clinical course observed in our patient, MCD was an unlikely diagnosis.

High-resolution CT findings in patients with IgG4-RD have been classified into four types: solid nodular, round-shaped ground glass opacity, alveolar interstitial, and bronchovascular types (7). However, the infiltrative type, as in our patient, has not been clearly described. There have been several case reports of patients with IgG4-RD exhibiting organizing pneumonia (8-12). However, pulmonary lesions have not been included in the diagnostic criteria for IgG4-RD (13). It is therefore necessary to evaluate additional patients with IgG4-related pulmonary disease to establish the diagnostic criteria for this condition.

IgG4-RD generally responds well to steroid therapy, which is often started at an intermediate dose of 30 mg/

day (2). After steroid tapering, however, the disease may relapse, with relapse rates of 32% within six months and 52% and 92% within 1 and 3 years, respectively (14). We combined a steroid with AZA, a drug shown to be effective in treating AIP and IgG4-associated cholangitis (15, 16).

It is known that the effectiveness of corticosteroids is usually evaluated according to the improvement of clinical symptoms and radiological findings, and serological markers may not reflect the condition of IgG4-RD (14). In the present case, MTX was considered to be ineffective because the patient's clinical symptoms and radiographic findings did not improve. However after the administration of AZA, both the symptoms and radiological findings quickly improved, and no recurrence has been observed despite tapering of PSL to 10 mg/day. We thereby speculate that improvement of the disease was due to the effect of AZA.

The action mechanism of AZA has not been fully elucidated due to complex metabolic pathways and the genetic polymorphisms in metabolizing enzymes (17). AZA is nonenzymatically rapidly converted to 6-MP, acting as a purine analogue and an inhibitor of DNA and RNA synthesis. By this process, the proliferation of both T cells and B cells are suppressed, and AZA shows immunosuppressive and anti-inflammatory effects (18).

Conversely, the anti-inflammatory effect of MTX is mainly due to the suppression of adhesion and activation of T cells. It has been suggested that the ineffectiveness of MTX and responsiveness to AZA treatment were due to the involvement of B cells in IgG4-RD (19).

The combinations of steroids with cyclosporine, AZA, mycophenolate mofetil, rituximab, and MTX have also been found effective in patients with IgG4-RD (15, 16, 20-22), with cyclosporine reported to be the only agent effective in treating pulmonary lesions (11). Furthermore, we were unable to find any reports discussing the characteristics of steroid-resistant IgG4-RD. Further examination of additional patients is needed to select the appropriate immunosuppressants and determine criteria for their use in IgG4-RD patients.

We described a patient with IgG4-RD who exhibited organizing pneumonia and was successfully treated with a combination of PSL and AZA. The assessment of additional patients and establishment of diagnostic criteria for IgG4-RD are necessary to facilitate the diagnosis and treatment of this disease.

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

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