IgG4-related Lung Disease Associated with Autoimmune Hemolytic Anemia: A Case Report and a Literature Review

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Abstract

We herein report a case of IgG4-related lung disease (IgG4-RLD) associated with autoimmune hemolytic anemia (AIHA). A 73-year-old Japanese female visited our hospital for an examination following an abnormal chest X-ray in 1999. She was diagnosed with bronchiolitis and AIHA, and treatment with prednisolone was started. After seven years, she visited our department due to a cough. Chest computed tomography (CT) demonstrated focal consolidation with ground-glass attenuations and thickened bronchial walls in the bilateral lungs. She was clinically diagnosed and treated for bronchial asthma. CT findings had shown no changes, and a lung biopsy was performed using video-assisted thoracic surgery at eleven years from the first diagnosis of AIHA. The pathological findings demonstrated the presence of peribronchovascular lymphoplasmacytic infiltrates with stromal fibrotic changes, admixed with many IgG4-positive plasma cells. Furthermore, the patient’s serum IgG4 level was high, and her CT findings did not show any obvious abnormal findings in the any organs other than the lungs. She was diagnosed with IgG4-RLD based on the findings. We believe that this case report of IgG4-RLD associated with AIHA is clinically helpful for a better understanding of these diseases, although there are five reported cases of IgG4-related disease associated with AIHA.

Key words: IgG4-related lung disease, autoimmune hemolytic anemia, bronchiolitis, bronchial asthma

Introduction

IgG4-related disease (IgG4-RD) is a number of relatively new systemic disorders which are characterized by increased serum IgG4 levels, inflammation of IgG4-positive plasma cells and fibrotic changes in the affected area (1, 2). Recently, various organ diseases, which are associated with IgG4, including the lacrimal glands, the salivary glands, the pancreas, the kidneys and the lungs, have been reported (3, 4). IgG4-related lung disease (IgG4-RLD) accounts for approximately 10% of all cases of IgG4-RD (5) and various radiological patterns of pulmonary and pleural lesions have been reported (4, 6), since Taniguchi et al. reported the first case of interstitial pneumonia with autoimmune pancreatitis (AIP) (7). Although the number of IgG4-RD case reports has been increasing (6), to our knowledge, there are only five cases of IgG4-RD associated with autoimmune hemolytic anemia (AIHA) reported in the literature (8-12), and there are no reports of IgG4-RLD associated with AIHA. We herein report the case of a patient with IgG4-RLD associated with AIHA.

Case Report

A 73-year-old Japanese female initially visited our hospital for evaluation of an abnormal chest X-ray in July of 1999. She had never smoked and did not have any history...
Figure 1. The radiological findings of the present patient. A chest radiograph from 2006 (A), showing ground-glass attenuations (GGAs) in the bilateral upper lungs. The lung window of chest computed tomography at the same time (D and G), demonstrating focal consolidations with GGAs and thickened bronchial walls in bilateral upper lobes. The radiological findings on admission in 2010 (B, E and H), showing a slight improvement of pulmonary findings in comparison to 2006. The radiological findings demonstrated obvious improvement four months after the dosage of prednisolone was increased (C, F and I).

of relevant family diseases or allergic diseases. Chest computed tomography (CT) revealed focal consolidation and centrilobular nodules in the right upper and middle lobes. She was diagnosed with bronchiolitis based on the presence of a mild cough and the chest CT findings, and was indicated for observation without treatment. The patient’s anemia was observed to progress (hemoglobin 12.0→5.4 g/dL) in October of the same year and she was diagnosed with AIHA according to serum findings such as the elevation of indirect bilirubin (3.58 mg/dL), lactate dehydrogenase (1,543 IU/L) and the positive result of a direct Coombs test, in addition to anemia. Treatment with prednisolone (PSL) at a dose of 50 mg/day was started and tapered with the improvement of her anemia, to a dose of 2 mg/day. Thereafter, she received medical treatment in the department of hematology. She visited our department due to a dry cough in 2006. Chest CT revealed focal consolidation with ground-glass attenuations (GGAs) and thickened bronchial walls in the bilateral lungs (Fig. 1A, D, and G). The finding of anemia on a laboratory examination was not noted at this time. Wheezing was audible on chest auscultation and treatment with inhaled corticosteroid (ICS) and long-acting beta 2 agonist (LABA) was initiated to treat bronchial asthma. The number of eosinophils (5.0%) in the peripheral blood and immunoglobulin (Ig) E level (146 IU/mL) were within the normal ranges. The treatments led to the relief of her respiratory symptoms, however, the CT findings demonstrated no obvious improvement, and a flexible bronchoscopic examination was performed in October 2009. Transbronchial lung biopsy specimens which were obtained from the right S5 showed atypical bronchiolitis and mild inflammatory cell infiltration, while bronchoalveolar lavage fluid demonstrated an increase of lymphocytes (lymphocytes: 39.0%, eosinophils: 2.5%). A lung biopsy using video-assisted thoracic surgery (VATS) was then conducted in June 2010. On admission, the patient’s height was 157 cm and her body weight was 48 kg. Her body temperature was 36.8°C, her heart rate was 61 beats/min, her blood pressure was 121/68
mmHg, her oxygen saturation was 96% in room air and respiratory sounds on auscultation were normal. The laboratory findings on admission demonstrated a slight elevation of IgG (1,889 mg/dL), soluble interleukin-2 receptor (676 U/mL) and an increase of IgG4 (835 mg/dL). There were no obvious abnormal findings, including a relapse of anemia (Hb; 13.7 g/dL) in the peripheral blood cell counts or blood chemistry. In the immunological examination, the direct Coombs test was negative and rheumatoid factor, IgE, antinuclear antibody, soluble interleukin-2 receptor, angiotensin-converting enzyme, myeloperoxidase-anti-neutrophil cytoplasmic antibody (ANCA) and proteinase 3-ANCA were also all within the normal limits. A pulmonary function test showed a mild obstructive impairment (forced expiratory volume in one second; FEV₁₀₀ 1,550 mL, FEV₁₀₀ 56.4%, %FEV₁₀₀ 89.6%), however, her vital capacity (VC) was normal (VC 2,860mL, %VC 124.9%). A chest X-ray on admission showed GGAs in the bilateral upper lung fields. Chest CT on admission demonstrated heterogeneous GGAs with reticular or nodular shadows in the bilateral upper lobes and the bronchial wall thickness (Fig. 1B, E and H). These findings showed a slight improvement in comparison to the findings from 2006. Lung biopsy specimens obtained from the right S₁ and S₃ by VATS revealed the presence of peribronchovascular lymphoplasmacytic infiltrates with stromal fibrotic changes, admixed with many IgG4-positive plasma cells (Fig. 2). These findings were consistent with the diagnostic criteria of IgG4-RLD, according to the guidelines of the Japanese Ministry of Health, Labor and Welfare Research Groups (13). In addition, the CT findings from the head to the abdomen did not suggest AIP or other abnormalities in other organs. The patient was thus diagnosed with IgG4-RLD. Her PSL dosage was increased from 2 to 10 mg/day, and her chest CT (Fig. 1C, F and I) and laboratory findings (Fig. 3) promptly improved. The PSL dose was gradually tapered to 4 mg/day, and there was no recurrence of IgG4-RLD or anemia after the tapering of PSL.

Discussion

In the present patient, IgG4-RLD was finally diagnosed by VATS although 11 years had passed from her first visit when she presented abnormal chest CT findings to the definitive diagnosis.

Recently, there have been numerous reports of patients with IgG4-RD. To date, however, there are only six cases
with IgG4-RD associated with AIHA (including the present case) (Table) (8-12). It is reported that the clinical characteristics of patients with IgG4-RD were observed in middle-aged men (5, 13), who showed a good response to corticosteroid treatment (6). In the six cases with IgG4-RD associated with AIHA, similar characteristics were observed in age, gender, and the efficacy for corticosteroids, although the present patient was female (Table). The dose of corticosteroid was increased from 2 mg/day to 10 mg/day in this case. The 30-60 mg/day dose of corticosteroid is generally administered as an initial dose in IgG4-RD (6), including the previously reported five cases associated with AIHA (6, 8-11), although we chose to treat our patient with low-dose corticosteroid therapy to avoid the side effects of corticosteroid. With regard to the timing of the diagnosis of two diseases, four of these six cases were diagnosed at the same time. In the present case, the appearance of IgG4-RLD might precede AIHA, although the diagnosis of IgG4-RLD was made 11 years after the diagnosis of AIHA, because the abnormal chest CT findings of the present patient were observed four months before the onset of AIHA, although we could not confirm whether IgG4-RD actually preceded AIHA without a chest X-ray and/or CT findings before 2006. In relation to an association between IgG4-RD and AIHA, it has been reported that both diseases showed an improvement by corticosteroid therapy, whereas the metachronous occurrence of both diseases has also been reported (9). The symptoms of AIHA remained unchanged at the time of diagnosis of IgG4-RD in our patient. We speculate that corticosteroid therapy administered at the diagnosis of IgG4-RLD as one of the reason.

The combination rate of bronchial asthma has been reported in 6.0-14.1% of patients with IgG4-RD (6, 14), and patients with IgG4-RLD mimicking asthma have also reported (15). The chief complaint of our patient when she visited our department was a cough, and she was treated with ICS and LABA inhalation treatment due to the suspicion of bronchial asthma. Obstructive impairment has been detected in 24% of the lung function tests in patients with IgG4-RLD (6), and bronchiolitis associated with IgG4-RD has also been reported (16, 17). The patient’s symptom of chronic cough and obstructive impairment might be due to
IgG4-related bronchiolitis, in addition to the potential presence of allergic disease in IgG4-RLD.

In relation to the chest CT findings, Inoue et al. reported that GGAs, the thickening of the bronchovascular bundles and the interlobular septa, and solitary nodular lesions were the major CT findings in patients with IgG4-RLD, and noted that it is necessary to distinguish bronchovascular type IgG4-RLD from sarcoidosis or lymphoproliferative disorders (18). The present patient was considered to correspond to the ”bronchovascular type” on the basis of her CT findings. And the CT findings of the present case showed no association with the disease of other organs for 11 years. We re-examined the findings to better understand that isolated IgG4-RLD can occur, even though most cases involve AIP (19).

AIHA is a disease that causes hemolysis due to the binding of IgG antibodies to the erythrocyte membranes. The disease responds to corticosteroid therapy (10). The mechanisms of comorbidity of IgG4-RLD and AIHA are thus far unknown. There have been 15 reported merged cases of AIHA and interstitial pneumonia (20, 21), although there are no reports of IgG4-RLD associated with AIHA. A possible mechanism for the combination of AIHA and interstitial pneumonia has been hypothesized: Th2 cytokines might be associated with the pathogenesis of pulmonary fibrosis, and the promotion of humoral immunity induced by the Th2 cytokines becomes predominant, which thus leads to the production of autoantibodies, and results in the triggering of AIHA (22). Whereas, the expressions of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 and their regulatory cytokines IL-10 and transforming growth factor (TGF)-β are upregulated in the affected tissues of patients with IgG4-RLD (23), and there may be a link between IgG4-RLD and AIHA through the Th2 cytokines. But the subclass of IgG that is involved in the pathogenesis of AIHA is mainly IgG1 and partly IgG3, while IgG2 and IgG4 are not basically involved (10).

On the other hand, the relationship between hematological disorders, including lymphoma, other than AIHA and IgG4-RLD has also been reported (24-26). Whereas, some hematological disorders such as multicentric Castleman’s disease, present with high levels of serum IgG4 levels and an increase in the IgG4/IgG ratio in the lung and lymph node tissues, must be distinguished from IgG4-RLD (27). A correlation between the disease progression and the level of complement or immune complex has also been reported, although they were not measured in the present case (28). Thus, the correlation between hematological disorders, including AIHA, and IgG4-RLD remains unclear. Therefore, further studies are also necessary to clarify the relationship between AIHA and IgG4-RLD.

There are some limitations to consider regarding the clinical course of this patient. The chest X-ray and CT images before 2006, except for the report of the chest CT findings in 1999, were not available. Therefore, we could not evaluate the clinical course of the image findings in this patient before 2006, which were necessary to evaluate the efficacy of PSL 50 mg/day for lung disease. In addition, the measurement of the IgG and IgG subclass was not performed before 2009.

In conclusion, we present the case of a patient with IgG4-RLD associated with AIHA who was diagnosed by VATS lung biopsy. The case of the present patient suggests that, although rare, IgG4-RLD should be considered as a complication in patients with AIHA, and further study is necessary regarding the significance of the association between IgG4-RLD and AIHA. In addition, physicians should pay attention to the presence of bronchiolitis due to similarity between the symptoms of IgG4-RLD and bronchial asthma.

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

References


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