Pathologically Proven Spontaneous Remission of IgG4-related Retroperitoneal Fibrosis

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Abstract

Some forms of idiopathic retroperitoneal fibrosis (RF) have recently been considered to be a part of the spectrum of immunoglobulin G4 (IgG4)-related disease. This case report is the first description of a spontaneous remission in a patient with pathologically proven IgG4-related RF. Although the pathogenesis and long-term disease behavior of IgG4-related RF remains unknown, we believe that an initial assessment consisting of only careful monitoring might be one important strategy, especially in asymptomatic IgG4-related RF patients without nephropathy, while carefully monitoring these patients for the risk of recurrence.

Key words: retroperitoneal fibrosis, spontaneous remission, IgG4-related disease

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Introduction

Retroperitoneal fibrosis (RF) is a rare disease characterized by the development of inflammation and fibrosis in the soft tissues of the retroperitoneum and other abdominal organs (1). The radiologic findings of a soft-tissue mass surrounding the abdominal aorta and the iliac arteries, with the possible encasement of neighboring structures, such as the ureters and the inferior vena cava, usually suggests a diagnosis of RF (2). Recent reports have shown that to some extent, that cases of idiopathic RF included immunoglobulin G4 (IgG4)-related RF (3). However, the concept of IgG4-related disease is relatively new, and few studies have so far been published on this disease. Patients with RF and associated with clinical symptoms (e.g., fatigue, weight loss, abdominal or back pain) or those with hydronephrosis and acute renal failure caused by ureteral obstruction usually require steroid therapy, regardless of the cause of RF (4). Therefore, the natural course of this disease remains unknown. We herein report a pathologically proven case of a spontaneous remission of IgG4-related RF.

Case Report

A 72-year-old man who was an ex-smoker (3 packs/day for 42 years) had no known history of dust exposure including asbestos. He had a medical history of cerebral infarction 10 years perviously and chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) of 46.8-57.1 mL/min/1.73 m² for the past 2 years]. He initially presented with complaints of fever, cough, and right-sided chest pain for one week and was then referred to our hospital.

The physical examination on admission did not reveal any eruptions or swelling of joints, superficial lymph nodes, lacrimal glands, or salivary glands. His body temperature was elevated at 38.6°C. An enhanced computed tomography (CT) scan revealed slight bilateral pleural effusion, a soft tissue mass surrounding the abdominal aorta, and bilateral hydronephrosis caused by sequential thickening of the retroperitoneum with encasement of both ureters, which were suspected to indicate RF (Fig. 1A-C). No other abnormalities, such as lymphadenopathy or abnormal kidney findings (e.g., multiple low-density areas, hypovascular solitary mass, hypertrophic renal pelvic wall) were revealed. The laboratory findings were as follows: leukocyte count 11,000/
μL (74.7% neutrophils, 12.5% lymphocytes, 9.5% monocytes, and 3.1% eosinophils), hemoglobin 13.1 g/dL, thrombocytes 37.5x10^4/μL, creatinine 1.01 mg/dL (eGFR of 56.2 mL/min/1.73 m^2), total bilirubin 0.4 mg/dL, and elevated levels of aspartate aminotransferase of 62 IU/L, alanine aminotransferase of 61 IU/L, gamma-glutamyl transpeptidase of 91 IU/L, alkaline phosphatase of 404 IU/L, lactate dehydrogenase of 255 IU/L, C-reactive protein (CRP) of 18.16 mg/dL, erythrocyte sedimentation rate of 114 mm/h, immunoglobulin G (IgG) of 2,515 mg/dL, IgG4 of 185 mg/dL, and soluble interleukin (IL)-2 receptor of 1,490 U/mL.

IL-6 was not elevated at <8 pg/mL. Anti-nuclear antibody was less than 40 titers according to immunofluorescence testing, and no other autoantibodies including anti-SS-A, anti-aminocyl tRNA synthetase antibody, rheumatoid factor, or anti-cyclic citrullinated peptide antibody were detected.

We initially started antibiotic therapy with ceftriaxone (2.0 g/day) because of the possibility of bacterial pleurisy as indicated by the clinical symptoms and existence of the pleural effusion. At the same time, because we suspected RF based on his radiological findings, we discontinued the aspirin he was taking to prevent a recurrence of cerebral infarction and began heparin bridging therapy before performing a biopsy on this patient to obtain a definitive diagnosis. After 1 week, the patient’s condition improved slightly, his CRP level decreased to 10.15 mg/dL, and antibiotic therapy was thus stopped. We then performed a CT-guided biopsy of the mass lesion surrounding the abdominal aorta (Fig. 2). The biopsy samples from the retroperitoneal mass showed lymphoplasmacytic infiltration and fibrosis, and the infiltration of IgG4+ plasma cells with a ratio of IgG4+/IgG+cells > 50%. Storiform fibrosis was also present (Fig. 3). Therefore, we diagnosed the patient to have IgG4-related RF. During this hospitalization for the biopsy, his initial symptoms (including fever, cough, and right-sided chest pain) improved, and his serum CRP level decreased to 2.51 mg/dL on the 14th hospital day. In addition, as there was no apparent worsening of his kidney disease, he was therefore discharged from the hospital. Immediately after discharge, he underwent an ^18F-fluorodeoxyglucose (FDG)-positron emission tomograph (PET)/CT scan, which showed a mild FDG uptake [standardized uptake value (SUV)max 3.5] within the retroperitoneal mass, but no other suspicious findings of IgG4-related disease. Therefore, we considered the possibility of this patient having both IgG4-related pleurisy as the cause of his pleural effusion and IgG4-related kidney disease as the cause of his CKD to be low, and thus we diagnosed RF as a single IgG4-related lesion.

At 2 months following the diagnosis of IgG4-related RF, he had no complaints, and his CRP level had decreased to within the normal range, and his IgG4 had also decreased to 41 mg/dL. Moreover, radiological findings showed an improvement of the retroperitoneal lesions (Fig. 1D-F). He recently underwent a follow-up outpatient examination that showed no relapse of RF for 10 months.

**Discussion**

RF is a rare syndrome hallmarked by fibrosclerotic tissue in the retroperitoneum, often leading to encasement of the ureters (5). RF is generally divided into two types: idiopathic RF, for which no clear cause is known, and secon-
Figure 2. Computed tomography (CT)-guided percutaneous needle biopsy for muddiness of the retroperitoneal mass lesion (dotted circle). (A) Marking of the biopsy entry site on the CT image in the prone position. (B) CT guided percutaneous fine needle aspiration biopsies using 18G cutting needles.

Figure 3. Histopathological findings of the retroperitoneal mass lesion. Lymphoplasmacytic infiltration and fibrosis were seen (A) [Hematoxylin and Eosin (H&E) staining, ×200]. Storiform fibrosis was also present (B) (H&E staining, ×400). IgG immunohistochemical staining revealed that most of the infiltrating plasma cells were positive (×400). IgG4 immunohistochemical staining revealed that more than 50% of the IgG-positive plasma cells were positive for IgG4 (×400).

Idiopathic RF often shows manifestations of an autoimmune disease and it has been found to occasionally occur as an extrapancreatic lesion of autoimmune pancreatitis. More recently, some forms of idiopathic RF are considered to be a part of the spectrum of IgG4-related disease (5-9), which has newly been recognized to be a fibro-inflammatory condition characterized by several features: a tendency to form tumefactive lesions at multiple sites, a characteristic histopathological appearance, and often, but not always, an elevated serum IgG4 concentration (10). Umehara et al. reported the comprehensive diagnostic criteria for IgG4-related disease as fol-
Regulatory T cells secrete transforming growth factor-β, the Th2 cytokines IL-4, IL-5, IL-10, and IL-13. Activated inflammatory cells and allergic response may lead to secondary RF due to drug therapy, malignant tumors, or chronic infections. However, our patient was diagnosed as having idiopathic IgG4-related RF because the serum IgG4 levels strongly correlated with the disease behavior of RF; however, this case was not biopsy proven. Therefore, the present report describes what we believe to be the first case of a spontaneous regression of biopsy proven IgG4-related RF.

The precise mechanism of the spontaneous remission in our patient is unclear. In IgG4-related disease, serum autoantibodies including anti-lactoferrin, rheumatoid factor, or IgG4 antibodies and elevated levels of serum IgE are often detected, and therefore the pathogenesis of IgG4-related disease is generally assumed from autoimmune and allergic responses (13, 14). In terms of autoimmune response, although no specific antigen targets for the IgG4 antibodies have been identified in patients with IgG4-related disease, IgG4 antibodies can activate both complement via the alternate pathway and leukocytes and can induce leukocyte-dependent tissue damage (15). With regard to allergic response, there is a known association between the preferential Th2-type response and an increase in the expression of the Th2 cytokines IL-4, IL-5, IL-10, and IL-13. Activated regulatory T cells secrete transforming growth factor-β, which is responsible for the fibrosis seen in IgG4-related disease (16). We surmise that one of the reasons for this is that all types of cytokines might be regulated for an immune and allergic self-limiting response. In fact, some cases of a spontaneous regression of IgG4-related pulmonary and hepatic inflammatory pseudotumor have been reported similar to our case (17, 18).

In clinical practice, the first goal of treatment in RF is the relief of ureteral obstruction to prevent any significant impairment in the function of one or both kidneys. Recently, a conservative approach followed by the administration of medical therapy (e.g., steroids) has become popular (19), and therefore, the long-term disease behavior of untreated IgG4-related RF remains unknown. However, our patient spontaneously showed complete remission during the clinical course. Importantly, IgG4-related RF rapidly responds to steroid treatment (3, 8). Taking the long-term adverse effects of steroid therapy together with the rapid response to steroid treatment, careful observation to determine whether or not the renal function is worsening in preparation for initiating steroid treatment may be one important treatment strategy in asymptomatic IgG4-related RF patients without IgG4-related kidney disease. However, because the natural history may be unclear, care should be taken to check for any frequent relapse of IgG4-related disease over the long term (12, 20).

In conclusion, we herein described the first known case of a spontaneous remission of biopsy proven IgG4-related RF. Because RF is essentially a rare disease, and the concept of IgG4-related disease is unfamiliar to many clinicians, few studies have been published on IgG4-related RF. Although the pathogenesis and long-term disease behavior of IgG4-related RF remains unknown, it will be important to continue to accumulate data and evaluate many cases of IgG4-related RF and identify the optimal therapeutic strategies.

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

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