CASE REPORT

Thrombotic Thrombocytopenic Purpura in IgG4-Related Disease With Severe Deficiency of ADAMTS-13 Activity and IgG4 Autoantibody Against ADAMTS-13

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Introduction

IgG4-related disease is a recently recognized group characterized by elevated serum IgG4 levels and prominent lymphoplasmacytic infiltration of IgG4-positive cells into multiple organs (1). The condition was first described in relation to the pancreas (i.e., autoimmune pancreatitis [AIP] [2]), but since then many other inflammatory conditions associated with IgG4-related disease have been reported, including sclerosing cholangitis, sialadenitis, lymphadenopathy, retroperitoneal fibrosis, interstitial pneumonia, and tubulointerstitial nephritis (1,3,4). Laboratory findings in IgG4-related disease are commonly characterized by hypergammaglobulinemia and high levels of serum IgG and IgG4, and in addition, a high serum IgE level, peripheral eosinophilia, and hypocomplementemia are often observed (3,4). Thrombocytopenia in IgG4-related disease is rare, but a few cases of autoimmune thrombocytopenia have been reported in patients with AIP (5,6). We describe here, to our knowledge, the first case of acquired thrombotic thrombocytopenic purpura (TTP) in a patient with IgG4-related lung disease with severe defi-ciency of ADAMTS-13 activity and IgG4 autoantibody against ADAMTS-13.

Case Report

A 57-year-old man presented at a local hospital with a 5-month history of dry cough. He had experienced allergic rhinitis for a long time, but had not sought treatment. He had no history of smoking. He had worked as a car mechanic for 30 years and had been occupationally exposed to fine particles. A chest radiograph showed reticular shadows in the bilateral lungs. Whole-body computed tomography (CT) examinations revealed thickening of the bronchovascular bundles, centrilobular opacities in both lungs (Figure 1), and swelling of the hilar, submandibular, and cervical lymph nodes. Laboratory examinations revealed high levels of serum IgG (3,744 mg/dl), IgG4 (2,500 mg/dl, normal value <105), and IgE (1,280 IU/ml, normal value <250). Peripheral blood tests showed a hemoglobin level of 13.8 gm/dl, a white blood cell count of $7,280/\mu l$ (eosinophils 2.2%), and a platelet count of $189,000/\mu l$. Antinuclear antibody, rheumatoid factor, myeloperoxidase–antineutrophil cytoplasmic antibody (ANCA), proteinase 3–ANCA, and M protein were all negative. The titer of C-reactive protein was 0.12 mg/dl. Serum levels of KL-6, angiotensin-converting enzyme, and CH50 were normal. The serum level of soluble interleukin-2 (IL-2) receptor was elevated to 864 units/ml (normal value <500). Lung specimens obtained by video-assisted thoracic surgery revealed marked lymphoplasmacytic infiltration around the bronchioles (Figure 2). IgG4 immunostaining showed numerous IgG4-positive plasma cells (Figure 3), with an IgG4/IgG ratio of >40%. There was no deviation in the distribution of lymphoid cells positive for κ and λ light chains. The patient was diagnosed as having IgG4-related lung disease and was administered only steroid inhalation therapy because his symptoms were mild, and the dry cough improved with therapy.

Four months after diagnosis of IgG4-related lung dis-

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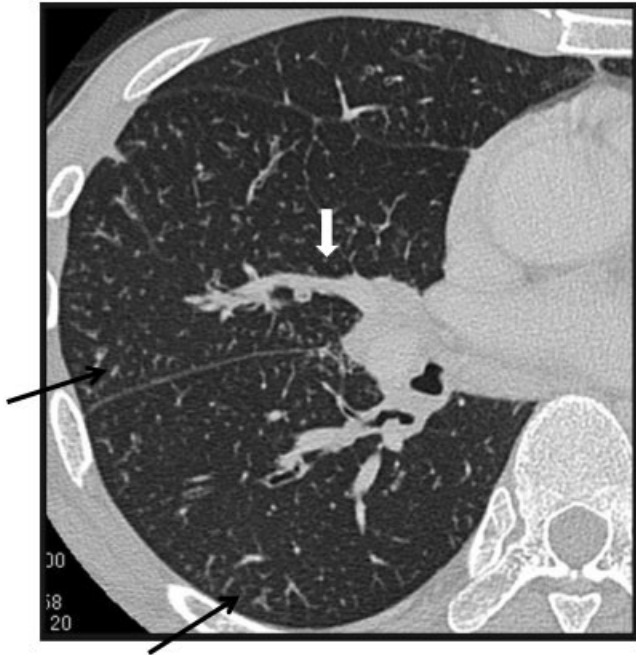Submitted for publication November 16, 2010; accepted in revised form April 13, 2011.

Figure 1. High-resolution chest computed tomography demonstrated thickening of the bronchovascular bundles (**white arrow**) and centrilobular opacities (**black arrows**).

ease, however, he noted general fatigue and petechiae on both legs. He was referred to our hospital because of progressive anemia and thrombocytopenia. On admission, his blood pressure was 109/77 mm Hg and his temperature was 36.2°C. The conjunctivae were anemic and icteric. There was no peripheral lymphadenopathy or neurologic signs, and no abnormalities were evident in the chest or abdomen. Laboratory examinations revealed the following: a hemoglobin level of 7.8 gm/dl, a white blood cell count of 6,000/μl (neutrophils 55%, lymphocytes 31%, eosinophils 4%, basophils 5%, and monocytes 4%), a platelet count of 17,000/μl (normal range 120,000–300,000), and reticulocytes of 13.3% (normal range 0.3–20). Urinalysis data were normal. The C-reactive protein level was 0.13 mg/dl, aspartate aminotransferase was 42 IU/liter (normal range 8–40), alanine aminotransferase was 35 IU/liter (normal range 5–45), lactate dehydrogenase was 513 IU/liter (normal range 105–215), total bilirubin was 2.0 mg/dl (normal range 0.2–1.2), direct bilirubin was 0.6 mg/dl (normal range 0.0–0.4), creatinine was 1.07 mg/dl (normal range 0.7–1.2), ferritin was 351 ng/ml (normal range 22–233), IgG was 3,087 mg/dl (normal range 870–1,600), IgG4 was 1,630 mg/dl (normal value <105), IgA was 126 mg/dl (normal range 110–410), and IgM was 55 mg/dl (normal range 35–220). Antinuclear antibody was negative and the complement levels were normal. The haptoglobin level was undetectable. Prothrombin time, activated partial prothrombin time, and plasma levels of fibrinogen, anti–thrombin III, plasminogen, and α_2-plasmin inhibitor were all within the normal ranges. The level of fibrin/fibrinogen degradation products was 4.1 μg/ml (normal value <5), that of D-dimer was 1.0 μg/ml (normal value <0.5), and that of platelet-associated IgG was 54 ng/10^7 cells (normal range 5.0–25.0). The Coombs' test

was negative. A bone marrow aspirate showed normal cellular marrow with erythroid hyperplasia and normal maturation of granulocytes and megakaryocytes. Whole-body CT examination showed abnormalities in the lung, which had remained unchanged for 4 months, but no abnormalities in other areas. Because anemia and thrombocytopenia improved spontaneously (the hemoglobin level and platelet counts increased to 9.5 gm/dl and 120,000/μl, respectively, at 10 days after admission), the patient was discharged. However, 7 days after discharge, his condition worsened again (hemoglobin level of 9.1 gm/dl and platelet count of 12,000/μl) and he was readmitted. Treatment with prednisolone 0.6 mg/kg/day (30 mg daily) was started, but the anemia and thrombocytopenia were not improved. Five days after readmission, the patient experienced mild disturbance of graphomotor function, and ADAMTS-13 (a disintegrin-like metalloproteinase with thrombospondin type 1 motifs 13) assays showed ADAMTS-13 activity <0.5% (normal range 70–
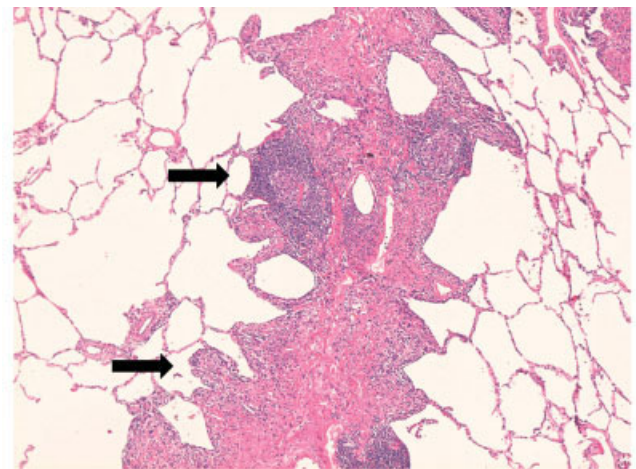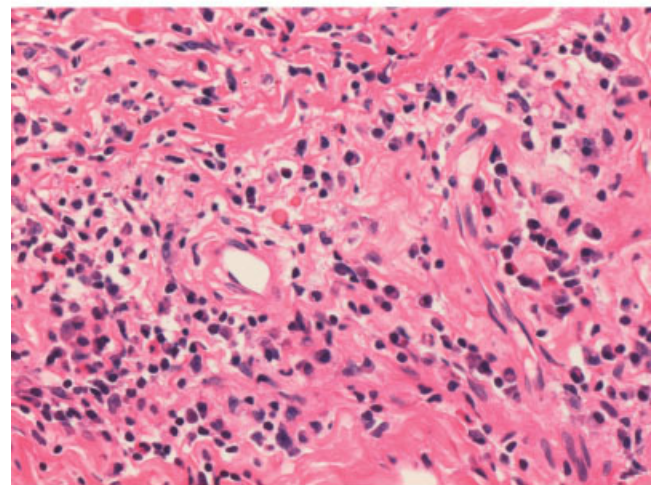
Figure 2. Microscopic features of lung specimens (hematoxylin and eosin stained). **A**, Marked inflammatory cell infiltration around the bronchioles (**arrows**; original magnification × 40). **B**, Inflammatory cells, consisting mainly of lymphocytes and plasma cells and some eosinophils (original magnification × 300).
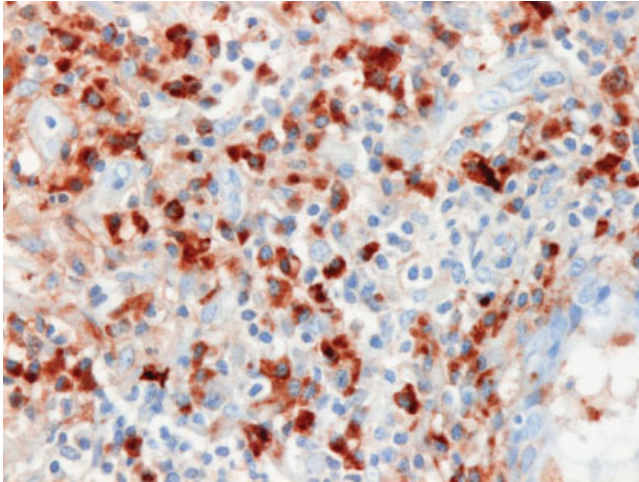
Figure 3. IgG4 immunostaining of a lung specimen, demonstrating numerous IgG4-positive plasma cells (original magnification × 400).

120) and ADAMTS-13 inhibitor of 3.3 Bethesda units/ml (normal value <0.5). He was diagnosed as having TTP and immediately received prednisolone at a dosage of 1 mg/kg/day (50 mg daily) concurrent with exchange plasmapheresis with fresh frozen plasma for 3 consecutive days. The platelet count increased immediately (110,000/μl at 3 days after 3 sessions of plasma exchange) and the hemoglobin level also improved. Thereafter, plasma exchange therapy was tapered and stopped (a total of 6 times) with continuation of steroid therapy. At 14 days after treatment, the hemoglobin level and platelet count increased to 12.0 gm/dl and 236,000/μl, respectively. The ADAMTS-13 activity increased to 37.6% and ADAMTS-13 inhibitor was not detected; the dose of prednisolone was then gradually tapered. One month after treatment, the hemoglobin level and platelet count were within normal ranges and the level of ADAMTS-13 activity was 50.5%. The serum levels of IgG and IgG4 decreased to 995 mg/dl and 207 mg/dl, respectively, and radiologic abnormalities in the lungs improved significantly. Ten months later, the patient was receiving 5 mg of prednisolone daily, and there was no recurrence of TTP and IgG4-related lung disease.

We analyzed the subclasses of anti–ADAMTS-13 antibodies by enzyme-linked immunosorbent assay (7) in a plasma sample obtained before therapy. The results showed an increased titer of IgG anti–ADAMTS-13 antibodies being 100% of the IgG4 subclass. IgG1–3, IgM, as well as IgA anti–ADAMTS-13 antibodies were negative.

Discussion

TTP is a rare but life-threatening disease, characterized by generalized microvascular occlusion due to deposition of platelet thrombi. TTP has been classically identified by a pentad of clinical features, including microangiopathic hemolytic anemia, thrombocytopenia, renal involvement, neurologic abnormalities, and fever. Recent studies, however, have revealed that severe deficiency of ADAMTS-13 is the major risk factor for TTP, and that clinical features such as renal failure, neurologic abnormalities, and fever are not necessarily essential for diagnosis (8). TTP is di-

vided into congenital, idiopathic, and secondary forms. In most patients with acquired idiopathic TTP, a deficiency of ADAMTS-13 activity is observed and autoantibodies against ADAMTS-13 are believed to be the major cause for this deficiency (8,9). In contrast, in patients with secondary TTP, the ADAMTS-13 activity varies from a marked reduction to normal, and the frequency of positivity for neutralizing antibodies against ADAMTS-13 (ADAMTS-13 inhibitor) also varies (9). Recently, our collaborators Ferrari et al analyzed the IgG subclass distribution of anti–ADAMTS-13 antibodies in 58 patients with acquired TTP (53 of 58 being idiopathic) with severely reduced (<10%) levels of plasma ADAMTS-13 activity (7). All of them had IgG anti–ADAMTS-13 antibodies, and IgG4 (52 [90%] of 58) was the most prevalent IgG subclass, followed by IgG1 (52%), IgG2 (50%), and IgG3 (33%). In a remarkable number of patients (17 of 52), IgG4 was the only subtype detected, suggesting a dominant role of IgG4 in acquired idiopathic TTP.

IgG4 is the least abundant IgG subclass in plasma, accounting for only 3–6% of total IgG in normal serum. Although high serum IgG4 concentrations have been reported in a few diseases (10), IgG4 has not been a focus of special interest. However, since Hamano et al reported high serum IgG4 concentrations in patients with AIP (2), high serum IgG4 levels with an abundant infiltration of IgG4-positive plasma cells into affected organs have been observed in various conditions (1), and now the new clinical entity of IgG4-related disease has been attracting worldwide attention (3). In the present case, the levels of serum IgG, IgG4, and IgE were markedly elevated. Thickening of bronchovascular bundles and centrilobular opacities were demonstrated in radiologic studies, and numerous IgG4-positive plasma cells were detected in the specimens obtained by lung biopsy, being compatible with IgG4-related lung disease (11). However, TTP in IgG4-related disease is extremely rare, and this appears to be the first case report.

Although a high serum IgG4 level and IgG4-positive plasma cell infiltration are characteristic, the pathogenesis of the disease has not been elucidated. The term "AIP" was first proposed by Yoshida et al (12) because of characteristics such as hypergammaglobulinemia, positivity for autoantibody, frequent complication with other autoimmune diseases such as Sjögren's syndrome, and a favorable response to steroid therapy suggesting autoimmune mechanisms. However, extrapancreatic lesions are associated with IgG4-related conditions and do not accompany other autoimmune diseases (3), the target autoantigen(s) and disease-specific autoantibodies so far remaining unidentified. It is still unclear whether IgG4-related disease falls within the category of autoimmune disease (3). However, thrombocytopenia in AIP, despite the limited number of cases, is considered to be associated with autoimmune mechanisms (5,6). In such cases, the levels of platelet-associated IgG are increased and thrombocytopenia is markedly improved with steroid therapy. Murase et al presented a patient with AIP complicated by thrombocytopenia in whom IgG4 and IgG1 antibodies against the platelets were demonstrated (6). Our present patient with TTP showed a severe deficiency of ADAMTS-13 with neu-

tralizing IgG4 autoantibody against ADAMTS-13 (IgG4 100%), suggesting that IgG4 antibody could act as a pathogenic autoantibody in IgG4-related disease under certain circumstances.

IgG4 is unique among the subclasses, as it is unable to bind C1q complement and has a low affinity for target antigens (10). It is a Th2-dependent IgG subclass, and IL-4 directs naive human B cells to switch to IgG4 and IgE production. IgG4 is predominantly produced after prolonged antigenic stimulation. In the context of IgE-mediated allergy, the appearance of IgG4 antibodies is usually associated with a decrease in symptoms, i.e., IgG4 acts as a "protective" antibody (10). In contrast, IgG4 autoantibodies from patients with pemphigoid diseases cause intraepithelial blisters by binding to their target antigen in the desmosome, i.e., acting as "pathogenic" antibodies (10). In IgG4-related disease, Th2 and regulatory cytokines and regulatory T cells have been shown to play an important role (13,14) similar to that shown in some allergic states, although the role of IgG4 in the pathogenesis remains unknown.

Although most types of organ involvement in IgG4-related disease respond well to steroid therapy (1,2,4), plasma exchange is essential for treatment of TTP (8). In fact, in the present case, steroid therapy alone was insufficient and plasma exchange was quite effective. Because TTP is life threatening, it is necessary to be aware that it can develop in IgG4-related disease and to measure ADAMTS-13 activity and inhibitor activity when a patient with IgG4-related disease shows thrombocytopenia and hemolytic anemia. Furthermore, relapse can occur in both IgG4-related disease and TTP. In particular, as high levels of IgG4 autoantibody against ADAMTS-13 with undetectable IgG1 are known to be associated with a tendency for recurrence TTP (7), we intend to follow up with our patient carefully for possible recurrence of both diseases.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saeki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Saeki, Ito.

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