Acquired Hemophilia A Associated with IgG4-related Lung Disease in a Patient with Autoimmune Pancreatitis

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Abstract

Immunoglobulin G4 (IgG4)-related lung diseases can occur in patients with autoimmune pancreatitis (AIP). However, the causal relationship between AIP and acquired hemophilia A (AH) is unknown. We herein report the first case of AH associated with IgG4-related lung disease that developed in a patient with AIP. A 65-year-old asymptomatic man with a history of AIP and sclerosing cholangitis diagnosed at the age of 57 was admitted to our hospital due to an abnormal reticulonodular shadow on chest X-ray. An examination of lung biopsy specimens revealed IgG4-positive plasma cell infiltration in the interstitium. The serum IgG4 level was elevated. One year later, the patient developed a progressive severe hematoma in the left femoral muscle. On admission, laboratory examinations revealed severe anemia with a markedly prolonged activated partial prothrombin time, a decreased level of factor VIII (FVIII) activity, and the existence of anti-FVIII antibodies. These findings were consistent with a diagnosis of AH. No relapse has been observed over the past 25 months, during which time, corticosteroid therapy has been continuously administered.

Key words: IgG4-related disease, IgG4-related lung disease, acquired hemophilia A, autoimmune pancreatitis


Case Report

Diffuse abnormal shadows were evident on a chest X-ray performed as part of a routine health check-up in a 65-year-old man. The patient developed bronchial asthma at 10 years of age and had also suffered from autoimmune pancreatitis (AIP), sclerosing cholangitis and diabetes mellitus since 57 years of age. A laboratory examination conducted on admission showed high levels of total protein (10.8 g/dL), immunoglobulin (Ig)G (8,688 mg/dL, normal range: 703-1,540), IgG4 (3,920 mg/dL, normal: <105), IgE (2,560 IU/mL, normal: <173) and sIL-2R (1,570 U/mL, normal range: 220-530). The results of peripheral blood tests were as follows: white blood cell count: 9,000/μL with 18.0% eosinophils, hemoglobin: 10.8 g/dL and platelet count: 325,000/μL. Multiple nodular lesions with thickening of bronchovascular bundles were evident in both lung lobes (Fig. 1). Lung biopsy specimens of the left S¹⁰c revealed a subpleural nodule containing marked lymphoplasmacytic infiltration with irregular fibrosis, narrow bronchioli surrounded by lymphoplasmacytic infiltration and obliterator phlebitis and arteritis accompanied by intimal and mural inflammatory cell infiltration corresponding to ground glass opacity and a subpleural small nodular lesion observed on high-resolution chest CT (HRCT) (Fig. 2). Lung biopsy specimens of the left S¹⁰c revealed a subpleural nodule containing marked lymphoplasmacytic infiltration with irregular fibrosis, narrowed bronchioli surrounded by lymphoplasmacytic infiltration and obliterator phlebitis and arteritis accompanied by intimal and mural inflammatory cell infiltration corresponding to the subpleural nodular lesion with spiculation observed on the chest HRCT. In addition, immunohistochemical staining for IgG4 revealed numerous IgG4-positive

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plasma cells with an increased IgG4/IgG ratio of more than 50% in the nodular lesion (Fig. 3). There were no deviations in the distribution of lymphoid cells positive for kappa and lambda light chain. Consequently, the patient was diagnosed as having IgG4-related lung disease. However, one year after the diagnosis of IgG4-related lung disease was made, the patient became aware of left femoral pain and swelling that subsequently resulted in his inability to walk. Laboratory findings on admission were as follows: hemoglobin: 5.8 g/dL, white blood cell count: 12,000/μL (neutrophils: 48%,
lymphocytes: 24.5%, eosinophils: 23.5%, basophils: 1% and monocytes: 3%), platelet count: 316,000/μL and reticulocytes: 75.8% (normal range: 5-20) (15.4×10^3/μL). The results of coagulation studies showed a prolonged activated partial prothrombin time (APTT) (58.3s, normal range: 24.0-40.0) with a normal prothrombin time (13.2 s, normal range: 11.4-14.4). In addition, a coagulation factor assay revealed a markedly decreased level of factor VIII (FVIII) activity of 2% (normal range: 60-150), while the other factor activity levels were within the normal ranges. A high-titer of FVIII inhibitor of 20 Bethesda units was observed on an anti-FVIII antibody assay. Therefore, a diagnosis of acquired hemophilia A (AH) associated with IgG4-related lung disease was made. The patient was treated with recombinant activated factor VII (NovoSeven, Novo Nordisk, Princeton, NJ, USA) and prednisolone (PSL) (initial dose of 60 mg/day). The hematoma in the left femoral muscle gradually resolved along with improvements in the markers of coagulation abnormalities, such as a normalized APTT level and an elevated FVIII level of 112%. Negative conversion of FVIII inhibitor occurred on the 59th hospital day. Moreover, the multiple nodular lesions present in both lungs immediately resolved. Subsequently, the dose of PSL was gradually reduced to 5 mg/day over eight months. No relapse has been observed during the subsequent 25 months.

**Discussion**

In 2001, Hamano et al. (1), reported that some patients with AIP exhibit elevated serum IgG4 values and increased numbers of IgG4-positive plasma cells in their tissues. However, the etiology of IgG4-related disease is not well understood. The present patient was diagnosed to have IgG4-related disease in accordance with the criteria proposed by Umehara et al. (2), which consist of the following: (1) a clinical examination shows characteristic diffuse or localized swelling or masses in single or multiple organs; (2) a histopathological examination shows elevated serum IgG4 concentrations (≥135 mg/dL); and (3) a histopathological examination shows (i) marked lymphocyte and plasmacyte infiltration and fibrosis and (ii) infiltration of IgG4-positive plasma cells with a ratio of IgG4/IgG positive cells >40% and >10 IgG4-positive plasma cells/HPF.

The overall immune response is mediated by T-helper cell
2 (Th2) reactions with possible involvement of regulatory T cells (Tregs). The expressions of Th2 cytokines (interleukin (IL)-4, IL-5 and IL-13) and Treg cytokines (IL-10 and transforming growth factor (TGF)-β) are upregulated in the affected tissues of patients with IgG4-related diseases (3). We therefore speculate that an upregulation of Th2 cytokines induces IgE antibody production and increases the number of eosinophils and that plasma cells stimulated by IL-10 and TGF-β provoke IgG4 antibody production and fibrosis, respectively.

AH is a rare but life-threatening hemorrhagic disorder caused by the spontaneous appearance of autoantibodies against FVIII (4). The development of FVIII autoantibodies in nonhemophilic patients can be associated with a variety of underlying conditions, including autoimmune diseases, malignancy, drug reactions, pregnancy or post-partum events (5). No associations between IgG4-related lung disease and AH have so far been described. FVIII autoantibodies may be oligoclonal in origin with a mixed composition of IgG subtypes that incorporate IgG1, IgG2, IgG4 and, more rarely, IgG3. IgG4 appears to be the dominant subtype (6). Recently, Saeki et al (7). reported that thrombotic thrombocytopenic purpura (TTP) occurs in patients with IgG4-related disease due to the existence of neutralizing IgG4-autoantibodies against ADAMTS13. Therefore, we suggest that IgG4 antibodies can act as pathogenetic autoantibodies in complicated diseases such as TTP or AH. Moreover, it is known that there is a strong association between IL-10G, located in the promoter region of the IL-10 gene, and the development of FVIII inhibitor (8). We believe that AH can be caused by IgG4-related disease; therefore, there is a close immunologic relationship between AH and IgG4-related disease.

In conclusion, this is the first reported case in which AH and IgG4-related lung disease were observed to overlap. In the future, it is important to focus on the role of IgG4 antibodies in order to understand the clinicopathological characteristics of IgG4-related diseases.

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

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