A Case of Aortic Stenosis with Serum IgG4 Elevation, and IgG4-Positive Plasmacytic Infiltration in the Aortic Valve, Epicardium, and Aortic Adventitia

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Summary
A 74-year-old man was admitted for preoperative screening of aortic stenosis. Five months before this admission, he was found to have elevated serum immunoglobulin G4 (IgG4; 2,010 mg/dL). Computed tomography (CT) showed a soft tissue mass surrounding the abdominal aorta, suggestive of IgG4-related periaortitis. CT coronary angiography showed perivascular thickening of the right coronary artery, and subsequent coronary angiography showed a multi-vessel disease. The patient underwent aortic valve replacement and coronary bypass surgery. Immunohistochemical analysis showed IgG4-positive plasmacytic infiltration in specimens from the aortic valve, epicardium, and aortic adventitia, suggestive of the possible role of IgG4-related immune inflammation for the pathogenesis.

Key words: IgG4-related disease, Pericarditis, Coronary periarteritis, Periaortitis

Immunoglobulin G4 (IgG4)-related disease is a relatively new clinicopathological disorder characterized by radiologic, serologic, and histopathologic findings, which may target a wide variety of organs, including the eye, lacrimal and salivary glands, respiratory system, and kidneys. IgG4 is, in general, considered to act protectively against excessive immune-mediated inflammation; therefore, IgG4 per se may not play a causal role in the development of IgG4-related disease.

Recent studies have shown that IgG4-related disease may also target cardiovascular systems, including the aorta, peripheral arteries, and pericardium. In addition, immunohistochemical analysis of the tissue specimens indicated that infiltration of IgG4-positive plasma cells may not be a rare occurrence in various cardiac and arterial disorders that are not diagnosed with IgG4-related disease, suggesting that IgG4-related immune-mediated inflammation may influence the development and/or progression of various cardiovascular disorders.

We herein report a patient with aortic stenosis (AS) and coronary artery disease who had an elevated serum IgG4 level, and IgG4-positive plasmacytic infiltration was demonstrated in surgical samples of the aortic valve, aortic adventitia, and epicardium.

Case Report
A 74-year-old man was admitted to the cardiology department for the diagnosis and treatment of AS. The patient had a history of bronchial asthma, diabetes, and esophageal cancer; the cancer had been surgically treated 13 years previously. Five months before the current admission, the patient was diagnosed to have hyper IgG4-globulinemia together with elevated serum IgG4 (2,010 mg/dL), but a hematological examination ruled out multiple myeloma. Computed tomography (CT) showed a soft tissue mass surrounding the abdominal aorta, suggestive of either IgG4-related periaortitis or retroperitoneal fibrosis (Figure 1A), although tissue sampling was not performed. In addition, severe AS was diagnosed by echocardiography, and the patient was admitted to the cardiology department.

On admission, his vital signs included a body temperature of 36.6 degrees C, blood pressure of 143/80 mmHg, and heart rate of 74 beats/minute. Chest X-ray showed a reconstructed gastric tube (Figure 1B), and electrocardiography showed complete right bundle branch block and q wave and ST-segment depression in several
precordial leads (Figure 1C). Echocardiography showed preserved left ventricular systolic function and stenosis in the aortic valve, with an estimated aortic valve area of 0.68 cm².

Laboratory studies showed a white blood cell count of 6,560 cells/μL, hemoglobin level of 10.7 g/dL, and platelet count of 42.3 × 10⁴ cells/μL. The eosinophil count was 8.8 and 2.9 g/dL, respectively, and thus the albumin/globulin ratio was markedly decreased (0.49). Serum C-reactive protein was 0.10 mg/dL, soluble interleukin-2 receptor was 936 U/mL (normal range 145-519 U/mL), and B-type natriuretic peptide was 255.6 pg/mL. Serum levels of IgG (3,983 mg/dL) and IgE (1,208 mg/dL) were normal. Serum IgG4 level was markedly elevated (10.5%, 689 cells/μL). Total protein and albumin were 8.8 and 2.9 g/dL, respectively, and thus the albumin/globulin ratio was markedly decreased (0.49). Serum C-reactive protein was 0.10 mg/dL, soluble interleukin-2 receptor was 936 U/mL (normal range 145-519 U/mL), and B-type natriuretic peptide was 255.6 pg/mL. Serum levels of IgG (3,983 mg/dL) and IgE (1,208 mg/dL) were normal. Serum IgG4 level was markedly elevated (2,010 mg/dL). The test result for antinuclear antibody was < 40x; anti-double-stranded DNA (4.2 IU/mL), anti-SSA (< 1.0 U/mL), and anti-SSB (< 1.0 U/mL) antibodies, and rheumatoid factor (10 IU/mL) were all within the normal range. Total complement activity (CH50) was elevated (71.5 U/mL (normal range 32-48 U/mL), whereas C4 and C3 were both within the normal range (107 and 21.8 mg/dL, respectively).

CT coronary angiography showed perivascular thickening of the right coronary artery (RCA) (Figure 2A-C). Subsequent invasive coronary artery angiography showed total occlusion of the left anterior descending artery and 75% stenosis of the RCA (Figure 2D, E). 18F-fluorodeoxyglucose (18F-FDG) positron emission CT showed non-local recurrence of esophageal cancer, and enhanced uptake of FDG in the right parotid gland, which was subsequently found to be non-malignant (Figure 3). FDG uptake was not increased at the calcified aortic valve (Figure 3C, D) or adventitia of the RCA (Figure 3E, F). The patient then underwent aortic valve replacement and coronary bypass surgery (left internal thoracic artery to LAD, saphenous vein graft to the RCA). Histopathologic analysis of samples of the aortic valve, aortic wall, and epicardium were performed.

The perivascular tissue of the coronary artery was not sampled. Immunohistochemical staining of these tissues with antibody-specific IgGs (DakoCytomation, Glostrup, Denmark; polyclonal, × 1,000) and IgG4 (NICHIREI-BIOSCIENCE, Tokyo, Japan; clone HP6025, × 2) was performed. The anti-FOXP3 antibody was used to detect regulatory T cells (Tregs).9 The number of immunopositive cells was counted in three high-power fields (HPFs) of prominently inflamed areas, and the average number of immuno-positive cells per HPF was calculated.9 In the aortic valve, fibrotic thickening and atherosclerotic changes were frequently detected (Figure 4A). Lymphoplasmacytic infiltration in the lamina propria was relatively sparse; however, there were occasional agglomerations of IgG4-positive cells (Figure 4B). IgG4-positive cells were detected at 53/HPF and the IgG4/IgG ratio was 85% (Figure 4C) in the aortic valve. There was slight fibrotic thickening of the adventitia of the thoracic aorta, but neither storiform fibrosis or obstructive phlebitis was observed. In the adipose tissue surrounding the thoracic aorta, there were several lymphoplasmacytic agglomerations (Figure 4D) with IgG4-positive cell infiltration (Figure 4E). IgG4-positive cells were detected at 63/HPF and the IgG4/IgG ratio was 85% (Figure 4F). In the pericardium, fibrous nodular thickening with lymphoplasmacytic infiltration was seen (Figure 4G, H). Lymphoid follicles were detected. IgG4-positive cells were widely distributed (Figure 4I), and IgG4-positive cells were present at 52/HPF and the IgG4/IgG ratio was 56% (Figure 4J). In addition, FoxP3-positive cells were found to be present in the aortic valve, periaortic regions, and pericardium (Figure 5).

Three months after the aortic valve replacement and coronary bypass surgery, serum IgG4 levels slightly decreased to 1,560 mg/dL, but remained at considerably high levels, suggesting that IgG4-positive plasma cells that had infiltrated the stenotic aortic valve could not exclusively explain the elevated serum IgG4 levels.

**Discussion**

We herein have reported a patient with elevated serum IgG4 levels, AS, and coronary artery disease who underwent aortic valve replacement and coronary bypass surgery. Radiologic findings suggested the presence of retroperitoneal fibrosis and coronary periarteritis, although
FDG uptake was not increased in these areas. Histopathologic analysis showed IgG4-positive cell infiltration in the stenotic aortic valve, adjacent aortic adventitia, and epicardial tissue.

Several previous studies have demonstrated that aortic valvular disease may occur in auto-immune disorders, and that IgG4-positive cell infiltration may sometimes be observed in various cardiovascular loci, including periaortic/periarterial regions, pericardium, and aortic valve. For example, IgG4-positive cell infiltration was reported to be observed in up to two-thirds of cases of inflammatory abdominal aortic aneurysm. IgG4-positive plasmacytic infiltration can be observed in the coronary adventitia and the pericardium.

There are also a few reports that have demonstrated IgG4-positive plasma cell infiltration in the aortic valve in patients with AS. Steiner, et al. showed infiltration of IgG4-positive cells in 13 stenosed aortic valves (7.3%) from a total of 178 aortic valve samples, although they did not measure serum IgG4 levels or assess IgG4-related diseases in other organs. In addition, by performing IgG4 immunostaining of 103 consecutive cardiovascular surgical samples from patients with various cardiovascular diseases, we reported that infiltration of IgG4-positive cells was observed, albeit to a mild extent, in 5 (21%) aortic valve samples from patients with AS. Furthermore, Maleszewski, et al. reported two cases of AS in which IgG4-positive infiltration was observed in the stenosed aortic valve. One of the patients Maleszewski, et al. reported was found to have IgG4-related pancreatitis and elevated serum IgG4 levels after the surgery. These findings collectively suggest that IgG4-positive plasmacytic infiltration in the aortic valve may not be an extremely rare occurrence.

It may then be questioned whether the current patient can be diagnosed with IgG4-related disease that affected multiple cardiovascular tissues. In several previous reports, IgG4-related cardiovascular disease was diagnosed when either IgG4-positive plasmacytic infiltration or elevated serum IgG4 was present alongside the suspected radiologic findings, or when IgG4-related disease-like radiologic findings were observed in the heart or vessels in association with IgG4-related disease diagnosed elsewhere in non-cardiovascular organs. On the other hand, cur-
Currently, unlike several other organs, cardiac valve-specific diagnostic criteria for the diagnosis of IgG4-related disease do not exist in Japan. Comprehensive criteria mandate all the following three features: radiologic findings (diffuse or localized swelling or masses), histopathologic findings in the cardiovascular tissue (lymphocytic infiltration, fibrosis, and IgG4-positive plasmacytic infiltration), and serologic findings (serum IgG4 ≥ 135 mg/dL). Therefore, despite the infiltration of IgG4-positive plasma cells and elevation of serum IgG4, our patient may not completely fulfill the diagnostic criteria. The characteristic histologic features, such as obliterator phlebitis and storiform fibrosis, are not observed in the current case.

The strength of the current study is that we demonstrated that IgG4-positive plasmacytic infiltration simultaneously occurred in multiple cardiovascular structures—the aortic valve, periaorta, and epicardium. Several previous studies also showed that IgG4-related pathologies may simultaneously influence multiple cardiovascular organs. Considering these findings together, IgG4-related immunologic reactions may have the potential to influence the development or the progression of systemic conditions.
IgG4-RELATED AORTIC STENOSIS

**Figure 5.** Expression of FoxP3 in the surgical samples. A: Aortic valve. B: Adventitia of the aortic wall. C: Epicardium. Original magnification, x 400 (A, C); x 100 (B).

cardiovascular abnormalities. This possibility should be examined in future studies.

Finally, we demonstrated the presence of FoxP3-positive cells in the aortic valve, aortic adventitia, and epicardium. It was recently reported that patients with severe AS had higher circulating Tregs, which decreased after the aortic valve intervention.90 Tregs are also involved in the pathogenesis of IgG4-related disease affecting various regions, including the aorta. Whether FoxP3-positive Tregs, together with IgG4, play a role in the development and progression of AS warrants further investigations.

What would be the new insight in this case presentation? In our patient, IgG4-positive plasmacytic infiltration was present concomitantly in the stenosed aortic valve, periaortic regions, and pericardium. These findings suggest that IgG4-related immune-mediated pathologies may simultaneously involve multiple cardiovascular structures leading to clinically significant phenotypes. In addition, despite the elevation of serum IgG4 levels, preoperative FDG-positron emission tomography (PET) did not demonstrate enhanced FDG uptake in any cardiovascular structures. Therefore, we could not identify IgG4-positive plasmacytic infiltration in the aortic valve before obtaining histologic samples. Although the influence of IgG4-positive cellular infiltration on the progression of aortic valve degeneration is yet to be investigated, we should be aware that IgG4-positive cell infiltration may occur in multiple cardiovascular structures in patients with elevated IgG4 levels. We may have to assess whether incidence of cardiovascular disorders, such as AS and coronary artery disease, are increased or decreased among patients diagnosed with IgG4-related disease in non-cardiovascular organs in future studies.

The current case is the first to report a patient with AS in whom serum IgG4 levels were measured and FDG-PET was performed before the aortic valvular replacement. The serum IgG4 level was only mildly decreased after the valvular replacement therapy (from 2,010 to 1,560 mg/dL), suggesting that the plasma cells that are overproducing IgG4 continued to exist in the patient, although their anatomic distribution could not be specified by FDG-PET. On the other hand, until the clinical importance of IgG4-positive cell infiltration in the aortic valve in the development of AS is understood, the routine measurement of serum IgG4 levels or FDG-PET for patients with AS is, basically, not recommended.

In conclusion, we demonstrated a patient with AS, coronary artery disease, and abdominal periaortitis with elevated serum IgG4. Immunohistochemical analysis showed IgG4-positive plasmacytic infiltration in the aortic valve, aortic adventitia, and epicardium, suggesting the simultaneous influence of IgG4-associated immune-mediated inflammation over various cardiovascular tissues.

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**Disclosures**

**Conflicts of interest:** None.

**Informed consent:** Informed consent about the case-report submission was obtained from the patient reported in the current study.

**References**

and intimal IgG4-positive cell infiltration in rapidly growing aortic aneurysm. SAGE Open Med Case Rep 2013; 1: 2050313X13496504.