IgG4-Positive Plasmacytic Infiltration in Aortic Wall and Aortic Valve Surgical Samples and Its Relation to Preoperative Serum IgG4 Levels

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Summary

The prevalence and extent of immunoglobulin G4 (IgG4)-positive cell infiltration were investigated in 282 surgical samples of aortic wall and aortic valve. Tissue infiltration of IgG4-positive cells was observed in 24 (17.3%) of 139 aortic valve samples and 46 (32%) of 143 aortic wall samples, and the condition of IgG4-positive cell infiltration > 30/hpf together with IgG4/CD138 ratio > 40% was observed in 2 (1.4%) of aortic valve samples and 14 (9.8%) of aortic wall samples. Among 275 patients, preoperative serum IgG4 level was available in 48 patients (50 samples), and it was > 135 mg/dL in only one patient. Of these 48 patients with serum IgG4 measurement, 29 patients had aortic valve stenosis and 12 had aortic aneurysm. Compared with 23 aortic stenosis patients without tissue infiltration of IgG4-positive cells in the aortic valve, six patients with IgG4-positive cell infiltration had a more prevalent smoking history (26% versus 83%) and borderline significantly higher serum IgG4 (median, 24.5 mg/dL versus 55.5 mg/dL), although either preoperative peak pressure gradient between left ventricle and aorta or aortic valve area did not differ significantly between groups. Compared with six aortic aneurysm patients without tissue infiltration of IgG4-positive cells in the aortic wall, six patients with IgG4-positive cell infiltration had borderline significantly higher serum IgG4 (median, 28.9 mg/dL versus 68.2 mg/dL). The current study showed that tissue IgG4-positive infiltration is not a rare occurrence in the aortic stenosis and aortic aneurysm. Clinical significance of tissue IgG4-positive cell infiltration in these patients requires further investigation.

(Key words: IgG4-related disease, IgG4-positive cell infiltration, Aortic stenosis, Aortic aneurysm)

Methods

Ethics Statement: The current retrospective study was approved by the Ethics Committee of Osaka Medical College and was conducted in accordance with the Declaration of Helsinki.

Specimens: In our previous study examining histological samples obtained during cardiothoracic surgery over a 1-year period, IgG4-positive cell infiltration was observed only in aortic wall and aortic valve samples. In this study, therefore, histological analysis of either the aortic valve or aortic wall was carried out on 282 consecutive histological specimens (143 aortic wall, 139 aortic valve) obtained from 275 patients who underwent cardiovascular surgery at the Department of Thoracic and Cardiovascular Surgery, Osaka Medical College, between August 2012 and to examine whether preoperative serum IgG4 levels, when available, were associated with IgG4-positive cell infiltration in these tissues.

IgG4-related disease is a clinicopathological disorder that is diagnosed essentially by histopathological and clinical findings, with the latter including elevated serum IgG4 (> 135 mg/dL) and characteristic radiologic imaging. Increasing numbers of case report or case series show that IgG4-related disease may target cardiovascular organs, including aorta, peripheral arteries, pericardium, and cardiac valves. On the other hand, when making definitive diagnosis of IgG4-related disease, histopathological confirmation is required, especially when using comprehensive diagnostic criteria (CDC). Diagnosis IgG4-related disease is, however, often difficult due to non-negligible risk of tissue sampling and scattered distribution of inflamed areas. We previously demonstrated in a preliminary study that tissue infiltration of IgG4-positive cell may be observed with the frequency of more than 10% in surgically resected samples of the aortic wall and aortic valve. The aim of the current study is to reassess IgG4-positive cell infiltration in aortic wall and aortic valve samples by a larger sample size and to examine whether preoperative serum IgG4 levels, when available, were associated with IgG4-positive cell infiltration in these tissues.
and December 2017. None of the subjects had been diagnosed or was suspected to have IgG4-related disease at the time of surgery. The samples analyzed in the current study included those analyzed in our previous study, corresponding to patients who underwent cardiothoracic surgery between January 2014 and December 2014.3,6

**Histopathological analysis:** Histological evaluation was carried out on formalin-fixed and paraffin-embedded specimens. Immunostaining was performed using antibody against IgG4 and CD138, as described elsewhere.7 IgG4-positive cell infiltration was graded as follows: negative, 0/10 higher power fields (hpf), 1-10/hpf, 11-30/hpf, 31-60/hpf, 61-100/hpf, and > 100/hpf, and ratio of IgG4/CD138 was calculated when > 10/hpf IgG4-positive cell infiltration was observed.

**Measurement of serum IgG4 level:** Serum samples were available in 48 patients (50 samples) who had been admitted to the department of cardiology for preoperative evaluation or other purposes before their admission to the department of the cardiothoracic surgery. Serum IgG4 levels were measured in these samples, which had been stored at −80°C until use.

**Assessment of concomitant atherosclerotic diseases:** In some patients, whether serum IgG4 differed according to the presence of coronary artery disease (CAD) or peripheral artery disease (PAD) was assessed. CAD was defined to be present when preoperative invasive coronary angiography showed significant coronary artery stenosis or occlusion or when the patient had previous percutaneous or surgical coronary intervention. PAD was defined to be present when ankle-brachial index examined preoperatively was decreased (< 0.9) at either bilateral sides or when the patient had previous percutaneous or surgical lower extremity intervention.

**Estimation of aortic valve area:** Aortic valve area was estimated by the results of transthoracic two-dimensional echocardiographic planimetry and the continuity equation.9

**Statistical analysis:** Statistical analysis was performed by SPSS statistics version 22.0 (IBM, Armonk, NY, USA). Baseline characteristics were assessed with standard descriptive statistics. Data were expressed as either the mean ± standard deviation, median and interquartile range (IQR), or number and percentage, unless described otherwise. Spearman’s rank correlation test was used to assess the correlation between two variables. Continuous data were compared by ANOVA or Mann-Whitney U test, when appropriate, and categorical parameters were compared by χ² test. A P-value of < 0.05 was considered to be statistically significant.

**Results**

**Histopathological findings in 282 samples:** First, 282 histological samples (143 aortic wall, 139 aortic valve) obtained from 275 patients (mean age, 72.0 ± 9.4 years; male subjects, 65.9%) were examined. The underlying cardiovascular disorders were aortic aneurysm (thoracic, 41; abdominal, 30; thoracoabdominal, 4), aortic dissection (64), arteriosclerosis obliterans (2), right aortic arch (1), annuloaortic ectasia (1), aortic stenosis (AS) (103), aortic regurgitation (AR) (18), and AS and AR (18). From seven patients, both aortic wall and aortic valve specimens were sampled.

IgG4-positive cell infiltration was observed in 70/282 (24.8%) samples (aortic valve, 24/139 [17.3%]; aortic wall, 46/143 [32%]). In addition, 29 (10.2%) and 19 (6.7%) samples showed tissue infiltration of IgG4-positive cells with the extent of > 10/hpf and > 30/hpf, respectively (Figure 1A, B). IgG4-positive cell infiltration was present in > 10/hpf with an IgG4/CD138 ratio above 40% in 19/143 (13%) of aortic wall samples and 3/139 (2%) of aortic valve samples (Figures 1, 2). IgG4-positive cell infiltration > 30/hpf together with IgG4/CD138 ratio > 40% was observed in 14 aortic wall samples (10 aortic aneurysm, four aortic dissection) and two stenotic aortic valve samples. Thus, we observed that IgG4-positive cell infiltration > 30/hpf with IgG4/CD138 ratio > 40% was present in 13% (10/75) of aortic aneurysm samples, 6.3% (4/64) of aortic dissection samples, and 1.7% (2/121) of AS samples (either with or without AR). Further, neither stenosis nor obstructive phlebitis was observed in AS samples with IgG4-positive cell infiltration.

**Analysis of patients in which preoperative serum IgG4 value was available:** Next, we analyzed the subgroup of patients for whom preoperative serum IgG4 values were available (48 patients, 50 samples). The underlying cardiovascular disorders were aortic aneurysm (thoracic, 5; abdominal, 5; thoracoabdominal, 2), aortic dissection (3), AS (25), AR (6), and AS+AR (4).

IgG4-positive cell infiltration of any extent was observed in 12 (24%) of 50 samples, and an IgG4-positive cell infiltration > 10/hpf was observed in two samples (Figure 3)-one was an aortic valve specimen from a 70-year-old male whose serum IgG4 level was 70.5 mg/dL (Figure 3A-D), and the other was an aortic wall specimen from a 67-year-old male whose serum IgG4 level was 232 mg/dL (Figure 3E-H).

**Relationship between atherosclerotic disease and serum IgG4:** We next examined and compared the serum IgG4 levels by the presence or absence of atherosclerotic disease-CAD and PAD (Table I). Eighteen (46%) among 39 patients with preoperative coronary evaluation had CAD, and 5 (14%) among 37 patients with preoperative evaluation of lower extremity ischemia had PAD. Serum IgG4 did not differ significantly according to the presence or absence of CAD or PAD (Table I).

**Serum IgG4 levels in patients from whom aortic valve samples were obtained:** Among 35 patients in whom preoperative serum IgG4 value was available and from whom aortic samples were obtained, serum IgG4 was borderline significantly higher among those with IgG4-positive cell infiltration in the aortic valve (median 55.5 mg/dL, IQR 32.3-89.1 mg/dL) compared with those who did not have such infiltration (median 24.1 mg/dL, IQR 13.6-52.1 mg/dL, P = 0.055 by Mann-Whitney U test).

It was found that IgG4-positive cell infiltration was observed only in stenotic aortic valve; therefore, patients with stenotic aortic valve (AS or AS + AR) were examined (Table II). Smoking history was significantly more prevalent in patients with tissue IgG4-positive cell infiltration, and serum levels of C-reactive protein and IgG4...
Figure 1. Grading of IgG4-positive cell infiltration among the study population. A: Extent of IgG4-positive cell infiltration in 282 specimens from all patients enrolled. B: Percentage of the 282 samples with the indicated extent of IgG4-positive cell infiltration. C: Extent of IgG4-positive cell infiltration in 50 specimens from 48 patients whose preoperative serum IgG4 data were available. t-a, thoracoabdominal; AS, aortic stenosis; AR, aortic regurgitation.

Figure 2. Histopathological findings of tissue samples obtained from patients with aortic aneurysm and aortic stenosis. A-D: Sections from a patient with aortic aneurysm. A: Elastica staining. B, C: IgG4 staining. D: CD138 staining. E-H: Sections from a patient with aortic stenosis. E: Hematoxylin eosin staining. F, G: IgG4 staining. H: CD138 staining. Original magnification, ×40 (A, B, E, F) and ×400 (C, D, G, H). Scale bars indicate 50 μm (A, B, E, F) and 500 μm (C, D, G, H). Preoperative serum IgG4 levels were not measured in these patients.

were significantly and borderline significantly higher among those with tissue IgG4-positive cell infiltration, respectively, compared with patients without such infiltration. Conversely, neither peak pressure gradient between left ventricle and aorta nor estimated aortic valve area differed significantly according to the presence or absence of tissue IgG4-positive cell infiltration.

Serum IgG4 levels in patients from whom aortic wall
samples were obtained: Among patients in whom preoperative serum IgG4 value was available and from whom aortic wall was obtained, serum IgG4 was borderline significantly higher among those with IgG4-positive cell infiltration in the aortic wall (median 56.9 mg/dL, IQR 26.2-114.5 mg/dL) compared with those who did not have such infiltration (median 28.9 mg/dL, IQR 13.2-40.1 mg/dL, P = 0.084 by Mann-Whitney U test).

It was found that IgG4-positive cell infiltration was observed in the aortic wall specimen of aortic aneurysm; therefore, patients with aortic aneurysm were examined (Table III). Among this subpopulation, neither smoking history nor serum C-reactive protein level differed significantly between patients with tissue infiltration of IgG4-positive cells and those without such infiltration. Preoperative serum IgG4 was found to be again borderline significantly higher among those with tissue IgG4-positive cell infiltration. One patient had an IgG4 >135 mg/dL; this patient was clinically suspected to have infected thoracic aortic aneurysm and has been reported elsewhere.7)

Discussion

In the current study, we showed that IgG4-positive cell infiltration was not a rare observation and was present in one-fourth (70/282) of aortic wall or aortic valve surgical samples, although most infiltrations were minor in their extent (<10/hpf), which is consistent with the previous findings.7 We also found that among patients with stenotic aortic valve or aortic aneurysm in whom preoperative serum IgG4 value was available, serum IgG4 was borderline significantly higher in patients with tissue infiltration of IgG4-positive cells than those without.

Recent studies showed that infiltration of lymphocytes and plasma cells into the stenotic aortic valve may not be a rare observation and that IgG4-positive cell infiltration can also be seen in the stenotic aortic valve.11,12 Steiner showed that mild (1-30/hpf) IgG4-positive cell infiltration was observed in 13/178 (7.3%) of calcified aortic valve.12 Maleszewski, et al. demonstrated two cases in whom dense IgG4-positive cell infiltration (>100/hpf) with IgG4/IgG ratio >50% was observed in the aortic valve.13 We also showed that IgG4-positive cell infiltration was observed in 25/139 (18%) of aortic valve samples. However, we cannot readily conclude that these lesions indicate IgG4-related aortic valvulopathy. In Japan, CDC is currently the only criteria diagnosing IgG4-related cardiac valvulopathy, which requires both histopathological evidence and high serum IgG4 level for the definitive diagnosis. In the current study, IgG4-positive cell infiltration >10/hpf with an IgG4/CD138 ratio above 40%, a condition that is required by the CDC, was demonstrated in 3/139 (2.1%) aortic wall specimens. However, histological findings lacked characteristic fibrosis, storiform pattern of fibrosis, which is another requirement by CDC for definitive diagnosis. In addition, serum IgG4 level of the patients who showed >10/hpf IgG4-positive cell infiltration with IgG4/CD138 ratio of >40% in aortic valve specimens was not available (Figure 1C).

It was found that among patients with stenotic aortic valve, those with IgG4-positive cell infiltration in the aortic valve had borderline significantly higher serum IgG4 levels than those without IgG4-positive cell infiltration (Table III). On the other hand, serum IgG4 levels remained within normal range in all patients with stenotic aortic valve. In Maleszewski, et al.’s report, one patient with dense IgG4-positive cell infiltration in the aortic valve showed normal range serum IgG4 (90 mg/dL),
The current study has several limitations. First, pre-operative IgG4 data were available for only a fraction of patients. Second, although serum IgG4 levels tended to be elevated serum IgG4 (> 1000 mg/dL). It is possible that serum IgG4 level may not be elevated when aortic valve is involved with IgG4-related disease are obtained. These criteria include “IgG4-positive cell infiltration of > 10/hpf” and “IgG4/IgG (CD138) ratio of > 40%” and the presence of storiform fibrosis and/or obliterator phlebitis. The number of infiltrated serum IgG4-positive cell required by these organ-specific criteria is higher than that set in the CDC. The problem is that it is sometimes difficult to judge the presence/absence of storiform fibrosis. It should be noted that the presence of storiform fibrosis is not an indispensable requirement in organ-specific criteria for diagnosing IgG4-related disease in several other organs.14-16 What would be the potential clinical importance of diagnosing IgG4-related vascular and valvular diseases? Several previous studies have reported a male predominance and older age in IgG4-related periaortitis, although the results were not uniform.17,20 In addition, the clinical course might differ between IgG4-related and non-related cases, although, again, the results were not uniform.20,21 In that sense, whether patients with IgG4-positive cell infiltration in the aortic wall or aortic valves will have future IgG4-related disease in non-cardiovascular organs and, conversely, whether patients with IgG4-related disease in non-cardiovascular organs are more susceptible for the degenerative disease in the aorta and aortic valves need to be clarified in future prospective analysis. The current study has several limitations. First, pre-operative IgG4 data were available for only a fraction of patients. Second, although serum IgG4 levels tended to be higher among patients who had tissue infiltration of IgG4-positive cell, cause and resultant relationship cannot be deter-

Table II. Comparison of Clinical Variables among Patients with Stenotic Valve Whose Preoperative Serum IgG4 Levels were Available

| Variables | IgG4 staining Negative (n = 23) | Positive (n = 6) | P-value |
|-----------|-------------------------------|-----------------|--------|
| Age, years | 72.2 ± 7.7                     | 69.5 ± 10.1     | 0.487  |
| Men, n (%) | 14 (60.9)                      | 6 (100.0)       | 0.137  |
| Body mass index, kg/m² | 22.0 ± 2.6                     | 21.9 ± 2.7      | 0.909  |
| Systolic blood pressure, mmHg | 132 ± 17                   | 117 ± 6         | 0.037  |
| Smoking history | 6 (26)                       | 5 (83)          | 0.018  |
| Chronic hemodialysis, n (%) | 4 (17.4)                     | 1 (16.7)        | > 0.99 |
| Medication |                              |                 |        |
| ACE inhibitors/ARB, n (%) | 11 (47.8)                    | 2 (33.3)        | 0.663  |
| Beta blockers, n (%) | 4 (17.4)                      | 0 (0.0)         | 0.553  |
| Calcium channel blockers, n (%) | 9 (39.1)                  | 4 (66.7)        | 0.364  |
| Diabetic medication, n (%) | 3 (13.0)                      | 2 (33.3)        | 0.269  |
| Statin, n (%) | 11 (47.8)                    | 2 (33.3)        | 0.663  |
| Loop/thiazide diuretics, n (%) | 4 (17.4)                    | 1 (16.7)        | > 0.99 |
| Aldosterone antagonist, n (%) | 1 (4.3)                      | 0 (0.0)         | > 0.99 |
| Laboratory data |                              |                 |        |
| White blood cell count, × 10⁹/μL | 5.6 (4.4-7.0)              | 6.0 (4.3-7.4)   | 0.813  |
| Eosinophil count, μL | 132 (89-324)                   | 86 (52-264)     | 0.192  |
| Hemoglobin, g/dL | 13.0 (10.1-13.6)              | 14.3 (12.5-15.1) | 0.071  |
| Platelet count, × 10⁹/μL | 201 (175-292)                 | 163 (125-208)   | 0.114  |
| Total protein, mg/dL | 6.7 (6.5-7.1)                 | 7.2 (6.8-7.6)   | 0.158  |
| Albumin, mg/dL | 4.0 (3.7-4.5)                 | 4.3 (3.8-4.7)   | 0.302  |
| A/G ratio | 1.4 (1.2-1.5)                  | 1.5 (1.2-1.6)   | 0.511  |
| ALT, U/L | 16.0 (9.0-21.0)                | 17.5 (8.0-31.0) | 0.733  |
| eGFR*, mL/minute/1.73 m² | 61.9 (42.7-74.5)           | 70.6 (60.3-79.0) | 0.235  |
| C-reactive protein, mg/dL | 0.08 (0.03-0.15)            | 0.19 (0.12-1.82) | 0.041  |
| Serum IgG4, mg/dL | 24.5 (15.9-32.9)              | 55.5 (32.3-89.1) | 0.071  |
| Echocardiographic data |                              |                 |        |
| LVDd (cm) | 4.8 (4.1-5.2)                 | 5.0 (4.5-5.5)   | 0.477  |
| LVEF (%) | 68 (62-73)                    | 60 (47-68)      | 0.090  |
| Peak pressure gradient between LV and aorta, mmHg | 71.2 (58.1-95.3)     | 94.6 (64.0-123.9) | 0.232  |
| Estimated aortic valve area, cm² | 0.79 (0.64-0.89)     | 0.76 (0.59-0.83) | 0.546  |

ALT indicates alanine transaminase; LVDd, left ventricular diastolic dimension; and LVEF, left ventricular ejection fraction.

whereas the other patient, who also had noncardiac organ involvement (autoimmune pancreatitis), had markedly elevated serum IgG4 (> 1000 mg/dL).13 It is possible that serum IgG4 level may not be elevated when aortic valve is the only region where IgG4-positive cell infiltration is present or the extent of infiltration is only minor.

Another important finding of the current study was that IgG4-positive cell infiltration of > 10/hpf with an IgG4/CD138 ratio of > 40% was observed in 19 (13.2%) of 143 aortic wall specimens. As in the aortic valve, unavailability of serum IgG4 level makes the diagnosis of IgG4-related aortitis/periaortitis by CDC difficult. Organ-specific criteria for diagnosing IgG4-related periaortitis/periaortitis and retroperitoneal fibrosis have recently been formulated in Japan (available at http://j-circ.or.jp/topics/IgG4_doc.pdf). In the new diagnosing criteria, IgG4-related aortic/arterial lesion can be diagnosed even without serum IgG4 levels when the histopathological findings compatible with IgG4-related disease are obtained. These criteria include “IgG4-positive cell infiltration of > 30/hpf” and “IgG4/IgG (CD138) ratio of > 40%” and the presence of storiform fibrosis and/or obliterator phlebitis. The number of infiltrated serum IgG4-positive cell required by these organ-specific criteria is higher than that set in the CDC.
IgG4-positive cells in aortic valve/aortic wall

Table III. Comparison of Clinical Variables among Patients with Aortic Aneurysm Whose Preoperative Serum IgG4 Levels were Available

| Variables                        | IgG4 staining | P-value  |
|----------------------------------|--------------|----------|
| Location of aneurysm             |              |          |
| Abdominal (n = 5)                | 3 (60.0)     | 2 (40.0) | 0.301   |
| Thoracic (n = 4)                 | 3 (60.0)     | 2 (50.0) |          |
| Thoracoabdominal (n = 2)         | 0 (0)        | 2 (100)  |          |
| Age, years                       | 65.0 ± 8.6   | 72.5 ± 8.3 | 0.156   |
| Men, n (%)                       | 6 (100.0)    | 5 (83.3)  | > 0.99   |
| Body mass index, kg/m²           | 24.4 ± 0.8   | 25.4 ± 1.6 | 0.211   |
| Systolic blood pressure, mmHg    | 143 ± 21     | 128 ± 23  | 0.277    |
| Smoking history                  | 4 (66.7)     | 4 (66.7)  | > 0.99   |
| Medication                       |              |          |
| ACE inhibitors/ARB, n (%)        | 3 (50.0)     | 5 (83.3)  | 0.545    |
| Beta blockers, n (%)             | 0 (0.0)      | 0 (0.0)   |          |
| Calcium channel blockers, n (%)  | 1 (16.7)     | 5 (83.3)  | 0.080    |
| Diabetic medication, n (%)       | 1 (16.7)     | 2 (33.3)  | > 0.99   |
| Statin, n (%)                    | 2 (33.3)     | 3 (50.0)  | > 0.99   |
| Loop/thiazide diuretics, n (%)   | 0 (0.0)      | 2 (33.3)  | 0.455    |
| Aldosterone antagonist, n (%)    | 0 (0.0)      | 0 (0.0)   |          |
| Laboratory data                  |              |          |
| White blood cell count, × 10³/μL | 6.1 (3.7-7.8)| 5.9 (4.9-7.2)| > 0.99   |
| Eosinophil count, /μL            | 138 (45-206) | 196 (138-266)| 0.240    |
| Hemoglobin, g/dL                 | 14.0 (13.0-83.5)| 13.7 (11.3-15.5)| 0.589    |
| Platelet count, × 10³/μL         | 179 (115-270)| 210 (128-339)| 0.818    |
| Total protein, mg/dL             | 7.0 (6.4-7.2)| 7.1 (6.7-7.3)| 0.818    |
| Albumin, mg/dL                   | 3.9 (3.4-4.1)| 3.8 (3.4-4.1)| 0.818    |
| A/G ratio                        | 1.3 (1.0-63.7)| 1.2 (1.0-1.5)| 0.589    |
| ALT, U/L                         | 21.5 (15.3-27.3)| 16.0 (7.8-37.5)| 0.310    |
| eGFR*, mL/minute/1.73 m²         | 0.1 (0.1-24.0)| 0.2 (0.1-3.1)| 0.818    |
| C-reactive protein, mg/dL        | 54.9 (33.8-77.4)| 55.1 (33.3-70.6)| 0.818    |
| Serum IgG4, mg/dL                | 28.9 (8.5-43.6)| 68.2 (32.6-156.0)| 0.095    |
| Echocardiographic data           |              |          |
| LVEDD (cm)                       | 4.3 (3.8-5.0)| 5.0 (4.5-5.1)| 0.132    |
| LVEF (%)                         | 65 (63-73)   | 66 (54-74)| 0.818    |

ALT indicates alanine transaminase; LVEDD, left ventricular diastolic dimension; and LVEF, left ventricular ejection fraction.

terminated as we did not investigate IgG4-positive cell infiltration in other organs. Third, although we focused on the aortic valve samples for the analysis according to the previous preliminary study, IgG4-positive cell infiltration has been reported also in other cardiac valves.55

In conclusion, among 282 surgically resected histological specimens (143 aortic wall, 139 aortic valve), 22 (7.8%) (aortic wall, 19 [13.2%]; aortic valve, 3 [2.1%]) showed IgG4-positive cell infiltration of > 10/hpf with an IgG4/CD138 ratio of > 40%, and 16 (5.7%) specimens (aortic wall, 14 [13.2%]; aortic valve, 2 [2.1%]) showed IgG4-positive cell infiltration of > 30/hpf with an IgG4/CD138 ratio of > 40%. Clinical significance of IgG4-positive cell infiltration in aortic walls and aortic valve, especially stenotic ones, needs further investigation because such conditions are not uncommon.

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Conflicts of interest: Authors do not have a financial relationship with the organization that sponsored the research.

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

Statement of originality and authorship responsibility: The manuscript is original and that no portion (including figures or tables) is under consideration elsewhere or has been previously published.

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