

# A clinicopathologic study of immunoglobulin G4-related sclerosing disease of the thoracic aorta

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**Objective:** Immunoglobulin G4-related sclerosing disease (IgG4-SD) has recently been reported to occur in the cardiovascular system and manifest as inflammatory abdominal aortic aneurysm. Thoracic aortic lesions are often associated with aortitis in several divergent etiologies. Thus, this study was performed to review thoracic aortic lesions from the aspect of IgG4-SD and to elucidate the clinicopathologic characteristics of this subgroup in the thoracic aorta.

**Methods:** The study comprised 125 patients, including 71 with thoracic aortic aneurysm (TAA), 44 with aortic dissection, 7 with Takayasu aortitis, and 3 with infectious aortitis. IgG4-SD was identified by diffuse infiltration of numerous IgG4-positive plasmacytes by immunohistochemical examinations. Clinicopathologic features were compared between IgG4-related and IgG4-unrelated lesions.

**Results:** Among the 125 patients, IgG4-SD was found in 5 patients with TAA but was not detected in the other subgroups of thoracic aortic lesion. IgG4-related TAA included one case of lymphoplasmacytic aortitis, 1 case of inflammatory aneurysm, and three cases of atherosclerotic aneurysms. Patients with IgG4-related TAA showed clinicopathologic features similar to patients with IgG4-SD: male gender, old age, history of bronchial asthma and allergies, elevation of white blood cell counts, C-reactive protein levels, and IgG4 and IgE concentrations (in one patient); eosinophilic infiltration, obliterative phlebitis, lymph follicle formation, and perineural inflammation. In addition, compared with IgG4-unrelated TAA, IgG4-related TAA was characterized by clinically more frequency of involvement of the aortic arch ( $P = .002$ ), saccular formation ( $P = .003$ ), and fibrous adhesion to surrounding tissue ( $P < .001$ ), and histopathologically thicker entire aortic wall and adventitia ( $P < .001$  each).

**Conclusions:** IgG4-SD is involved in 4% of all thoracic aortic lesions and uniformly presents in the form of an aneurysm with distinct histologic and clinicopathologic features. IgG4-SD represents one, albeit rare, etiology of TAA, especially those originating in the aortic arch. (J Vasc Surg 2010;■■:■■■.)

**Clinical relevance:** IgG4-related sclerosing disease is clinically characterized by high serum IgG4 concentrations, a predilection for adult males, steroid sensitivity, and frequent association with multiple organs. IgG4-related sclerosing disease can manifest in the cardiovascular system as chronic periaortitis. We examined 125 cases of thoracic aortic lesions and revealed that 4% of these were linked to the IgG4-related lesions with distinct clinicopathologic features; saccular form aneurysm, location of aortic arch, and frequency of autoimmune disease and allergic diseases.

The close relationship between immunoglobulin (Ig) G4 and fibrous sclerosing lesions was first reported with regard to sclerosing pancreatitis, also known as autoimmune pancreatitis.<sup>1</sup> We have performed several clinicopathologic studies on idiopathic sclerosing lesions with a focus on IgG4.<sup>2-6</sup> IgG4-related sclerosing disease (IgG4-SD) is clinically characterized by high serum IgG4 concentrations,

a predilection for adult men, and frequent association with multiple lesions in different organs, and is effectively treatable using corticosteroids.<sup>7</sup> Pathologic features include diffuse lymphoplasmacytic infiltration, irregular fibrosis, frequent eosinophilic infiltration, obliterative phlebitis, and numerous IgG4-positive plasmacyte infiltration.<sup>8,9</sup>

In the abdominal aorta, aneurysms can be separated into two basic types: atherosclerotic and inflammatory. Since the first description by Walker et al<sup>10</sup> in 1972, inflammatory aneurysm has been histologically characterized by diffuse inflammatory cell infiltration and irregular fibrosis, primarily occurring in the adventitia and involving an unknown etiology.<sup>1,12</sup> Sclerosing inflammation in the aortic wall sometimes extends into fibroadipose connective tissue around the aorta, and these cases are known as inflammatory abdominal aortic aneurysm (AAA) associated with retroperitoneal fibrosis.<sup>13</sup> We recently reported that IgG4-SD can occur in the cardiovascular system and can manifest as inflammatory AAA.<sup>14,15</sup>

In contrast to aneurysms affecting the abdominal aorta, thoracic aortic aneurysms (TAAs) tend to be less athero-

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Competition of interest: none.

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sclerotic, fusiform shaped, and characterized by absence of thrombus,<sup>16</sup> because medial degeneration is the most common etiology for TAA.<sup>17</sup> Medial weakening in the aorta is often due to medial laminar necrosis resulting from inflammatory processes. A number of inflammatory thoracic aneurysms with divergent etiologies and pathologic classifications have been described.<sup>18</sup> For example, Takayasu aortitis is seen as the prototypical aortitis aneurysm of the thoracic aorta and shows thick aortic walls with diffuse infiltration of lymphoplasmacytic cells.<sup>19</sup> Healed and old aortic dissections show thickening of the adventitia and adhesion to surrounding tissue, sometimes resembling inflammatory aneurysm. In addition, TAA due to aortitis may result in aortic dissection. The term "inflammatory TAA," as the counterpart of inflammatory AAA, should thus be used with caution after excluding the possibility of other types of TAA associated with aortitis, healed dissections, and the like.

We have previously described detection of IgG4-related AAA cases in inflammatory AAA.<sup>14,15</sup> In addition, one patient we encountered showed tumorous lesions around the right coronary artery.<sup>20</sup> We speculated that IgG4-SD in the thoracic aorta may appear as aneurysmal or tumorous lesions. Indeed, two patients with IgG4-SD involving the thoracic aorta have been reported more recently: one involved IgG4-related inflammatory aneurysm,<sup>21</sup> and the other involved aortic dissection with lymphoplasmacytic periaortitis.<sup>22</sup> Nevertheless, the clinicopathologic characteristics of IgG4-SD in the thoracic aorta remain unclear. We therefore reviewed thoracic aortic lesions to elucidate the clinicopathologic characteristics of this subgroup in the thoracic aorta from the perspective of IgG4-SD.

## PATIENTS AND METHODS

This study was approved by the Human Investigation Review Committee of the University of Kanazawa (No. 468) and Kanazawa Medical Center (No. 248) and conformed to the principles outlined in the Declaration of Helsinki.

**Patient selection and classification.** The surgical pathology files of Kanazawa University Hospital and Kanazawa Medical Center were searched for patients who had undergone thoracic aortic surgery between January 1, 1989, and December 31, 2009. The study group comprised 125 patients, and the originally prepared histologic slides were available in all cases.

Of these, 71 patients showed resection in the thoracic aorta due to dilatation of the aorta and were thus categorized as TAA. Pathologically, 45 TAAs were atherosclerotic (64%) and 24 (34%) were related to medial degeneration. Among the 71 TAA patients, one case with predominant adventitial fibrosis and adhesion to surrounding tissue was clinically classified as inflammatory aneurysm. Another case with massive lymphoplasmacytic infiltration into the whole aortic wall was previously diagnosed as lymphoplasmacytic aortitis.

Aortic dissection was diagnosed due to macroscopic findings of a false lumen containing fresh thrombus, hematoma, or granulation tissue in 44 patients, and pathologic examination showed dissection in the media with massive medial degeneration. The aortic dissections in 35 patients (80%) were found after acute chest pain and subsequent emergency surgery. Seven patients displayed Takayasu aortitis, according to patient age (<65 years) and established clinical criteria,<sup>18</sup> and presented typical clinical signs, including dyspnea, fever, or decreased pulse in the extremities.

Four patients with Takayasu aortitis showed TAA, and two showed diffuse sclerosis of the aorta. Five patients received corticosteroids preoperatively. These cases were confirmed based on light microscopic features such as patchy medial laminar necrosis rimmed by macrophages and occasional giant cells.

Infectious aortitis was identified in three patients (one patient with fungus and two patients with bacteria) based on serologic date and pathologic findings of massive suppurative changes, such as granulation tissue with infiltration of neutrophils.

We were unable to identify patients with isolated aortitis in this series, even in the large category of aortitis of the ascending aorta.<sup>18,19</sup> Isolated aortitis often causes aneurysmal shape due to thinning of the aortic wall caused by inflammatory changes, as histopathologically characterized by patchy areas of medial necrosis associated with infiltration of lymphocytes, plasmacytes, and histiocytes.<sup>19</sup> All histologic analyses in this study were performed by two pathologists (S.K and Y.Z) who were blinded to the clinical features of the samples.

**Clinical features.** For each patient, the medical record was reviewed retrospectively and the following data were recorded: age, gender, medical history, and preoperative diagnosis. We examined whether the patient had a history of cardiovascular, autoimmune, or pancreatic disease (autoimmune pancreatitis).<sup>9</sup> History of allergic disorders, such as bronchial asthma and drug allergy, was also examined because associations between IgG4-SD and allergic reactions have been suggested.<sup>20</sup>

All patients with TAA and Takayasu aortitis were under preoperative surveillance for 6 months to 2 years. Infectious aortitis was observed for 1 to 3 weeks preoperatively. For all except the 44 patients with aortic dissection, preoperative serologic findings for white blood cell (WBC) count and C-reactive protein (CRP) level were available  $\leq 1$  month before operation. In 35 patients with aortic dissection, preoperative serologic data did not reflect the long-term immune status because the patients first entered our hospitals in a state of rapid dissection requiring emergency surgery.

All patients underwent radiologic examination, such as angiography, computed tomography, or magnetic resonance imaging. Maximum luminal diameter of the aneurysm was calculated on radiologic imaging in each patient. Location of the aortic lesion was classified into ascending or descending thoracic aorta, or aortic arch. Only the main

location was considered in aortic lesions involving two to three areas. Postoperatively, most patients (30 with TAA, 22 with aortic dissection, all with Takayasu disease, and none with infectious aneurysm) were followed-up at our hospitals for 2 to 10 years.

**Pathologic findings.** Histopathologic examination was performed for explanted aortic walls. In surgical specimens, the entire aorta was available in about half of the patients with thoracic lesions (43 with TAA, 2 with aortic dissection, and all with Takayasu disease and infectious aneurysm). Tissue samples from each surgically resected specimen were fixed in neutral formalin and embedded in paraffin in a mean of 5.5 sections (range, 3-9). An additional set of 4 to 6 sections (4-mm thick) was cut from each paraffin block. Some of these sections were stained with hematoxylin and eosin, elastica van Gieson, and Alcian blue; the rest were used for immunohistochemical investigations.

We histologically examined the following eight histologic features: adventitial thickness; infiltration of plasma cells, eosinophils ( $>5$  per high-power field [hpf]), and neutrophils ( $>10$  per hpf); lymph follicles with germinal center; obliterative phlebitis; perineural inflammatory cell infiltration; granuloma formation; presence of giant cells; and medial degenerative necrosis. Adventitial thickness (from the lowest elastic fiber of the media to the lowest part of the adventitia) at three sites in each case was calculated on elastica van Gieson-stained sections using a microscopic measure. Medial degenerative necrosis was defined as fragmentation or loss of elastic fibers, or both, associated with pools of glycosaminoglycans using Alcian blue-stained sections. Laminar medial coagulation was defined as localized coagulative necrosis of the media.

**Immunohistochemistry for IgG and IgG4.** Immunostaining of IgG and IgG4 was performed by an autostainer (HX System Benchmark, Ventana Medical Systems, Tucson, Ariz) following the manufacturer's instructions. Rabbit monoclonal antibody against human IgG (Dako Cytomation, Glostrup, Denmark) and mouse monoclonal antibody against human IgG4 (ZYMED Laboratory, San Francisco, Calif) were used as primary antibodies. Sections were pretreated with proteinase. Negative controls were evaluated by substituting the primary antibody with similarly diluted nonimmunized mouse serum. IgG-positive and IgG4-positive plasmacytes were counted in five different hpf ( $\times 10$  eyepiece,  $\times 40$  lens) in the more prominently inflamed areas in the aneurysm wall. The ratio of IgG4-positive cells to IgG-positive cells was calculated in each case. This study defined IgG4-SDs as those possessing numerous IgG4-positive plasmacytes, with  $>80$  IgG4-positive plasmacytes per hpf and a IgG4-positive/IgG-positive cell ratio  $>70\%$ .<sup>14,15</sup>

**Statistics.** Statistical analyses were performed using the Fisher test, the  $\chi^2$  test with the Yates correction when appropriate, and the Mann-Whitney rank sum test for unpaired nonparametric data. Values of  $P < .05$  were considered statistically significant.

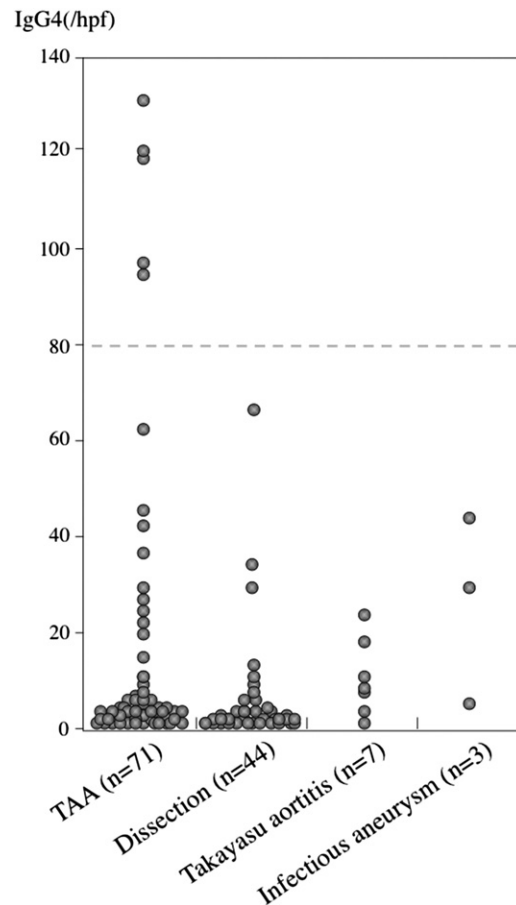


Fig 1. Distribution of plasma cells positive for immunoglobulin G4 (IgG4) in thoracic aortic lesions.

## RESULTS

**Selection of IgG4-related lesions in thoracic aortic lesions.** Using immunohistochemistry for IgG and IgG4 in all 125 patients with thoracic aortic lesions, we identified 5 patients with TAA showing diffuse infiltration of  $>80$  IgG4-positive plasmacytes per hpf (mean, 110.8/hpf; range, 90.3-133.3/hpf; Figs 1, 2). In the same cases, rates of IgG4-positive/IgG-positive cells were  $>70\%$  (mean, 77.4%; range, 70.5%-85.5%). These five patients with TAA with infiltration of numerous IgG4-positive plasmacytes were categorized as IgG4-TAA in this study (Table I). The IgG4-TAA group included one patient with inflammatory aneurysm (patient 1), one patient with lymphoplasmacytic aortitis (patient 2), and three patients with atherosclerotic TAA (patients 3, 4, and 5; Table I). We did not detect high concentrations of IgG4-positive plasmacytes in the other three groups, which represented aortic dissection, Takayasu aortitis, and infectious aortic aneurysm. Thus, IgG4-SD occurred in TAA and comprised 7.0% of TAAs and 4.0% of all resected thoracic lesions. The remaining 66 patients with TAA were assessed as non-IgG4-TAA in this study.

**Pathologic features of IgG4-related TAA.** We next compared the pathologic features of IgG4-related TAA,

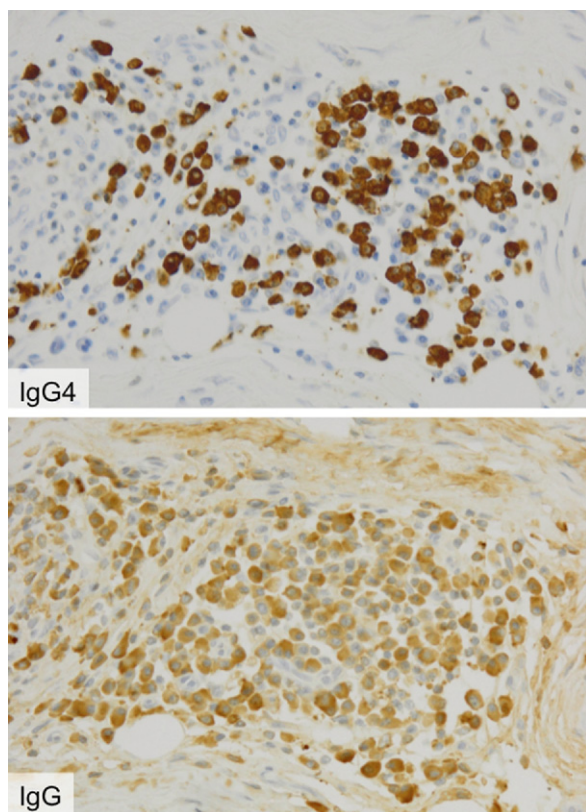


**Fig 2.** Immunohistochemical findings of immunoglobulin (Ig)G4-related thoracic aortic aneurysm (patient 11). Numerous IgG-positive and IgG4-positive plasma cells were detected in the adventitia. **Upper panel,** IgG4; **Lower panel,** IgG (original magnification  $\times 300$ , in almost the same field).

nonrelated TAA, aortic dissection, Takayasu aortitis, and infectious aortic aneurysm (Table II).

Mean thickness of the entire aortic wall was 6.5 mm (range, 5.0-9.0 mm) in IgG4-TAA and 4.3 mm (range, 2.4-8.5 mm) in non-IgG4-TAA. Mean adventitial thickness was 4.2 mm (range, 3.1-5.1 mm) in IgG4-TAA and 1.4 mm (range, 0.1-5.0 mm) in non-IgG4-TAA. The entire aortic wall and adventitia were significantly thicker in IgG4-TAA than in nonrelated cases ( $P < .001$  each). In IgG4-TAA, inflammatory cell infiltration was diffusely observed in the media and adventitia of the aortic wall, spreading to adjacent fibrous tissue. Inflammation predominantly involved lymphocytes and plasmacytes and was associated with irregular or storiform fibrosis (Fig 3).

Each patient with IgG4-TAA showed differing degrees of inflammatory cell infiltration and fibrosis. Patient 1, who had an inflammatory aneurysm, showed the densest fibrosis with scattered lymphoid follicles, whereas patient 2, with lymphoplasmacytic aortitis, showed the most massive infiltration of inflammatory cells from the media to the adventitia. The results for the remaining three patients (patients 3, 4, and 5) were somewhere between these two patients. Plasmacytes ( $>10/\text{hpf}$ ) were also observed in 73% of non-

IgG4-TAA; however, inflammation in non-IgG4-TAA was focally pronounced or associated with lymph nodes surrounding the aortic wall, not diffuse as in IgG4-TAA cases. Eosinophilic infiltration ( $>10/\text{hpf}$ ) was more commonly observed in IgG4-TAA compared with non-IgG4-TAA ( $P < .001$ ). In addition, IgG4-TAA was more frequently associated with lymph follicles ( $P = .005$ ), obliterative phlebitis ( $P < .001$ ), and inflammatory extension ( $P < .001$ ). In IgG4-TAA, we found rather small lymphoid follicles and inflammatory cell clusters dispersed throughout the media to adventitia. All cases of IgG4-TAA showed moderate to severe atherosclerosis. Epithelioid granuloma, giant cells, and medial necrosis were rare in cases of both IgG4-TAA and non-IgG4-TAA.

Overall aortic wall thickening with fibrosis and/or inflammatory changes was not common in most cases of aortic dissection. Compared with IgG4-TAA, infiltration of neutrophils and granulomas with foreign body giant cells were often detected in aortic dissection. Interestingly, the aortic dissection in five patients (11%) showed adventitial thickness  $>3$  mm (mean, 4.4 mm; range, 3.1-5.0 mm). Plasmacyte infiltration with lymphoid follicles and neutrophil infiltration was often detected in these patients. However, eosinophil infiltration and perineural infiltration was only seen in one patient, and obliterative phlebitis was not found.

Takayasu aortitis showed relative thickening of the entire aortic wall (mean, 4.6 mm; range, 3.0-7.1 mm) and adventitia (mean, 2.2 mm; range, 0.3-4.0 mm), but adventitial thickness was significantly higher in IgG4-TAA than in Takayasu aortitis ( $P = .019$ ). Takayasu aortitis was characterized by inflammatory cell infiltration predominantly affecting the media to the adventitia, so plasmacyte infiltration and lymphoid follicles were also often detected in Takayasu aortitis. Eosinophil infiltration, perineural infiltration, and obliterative phlebitis were not found in Takayasu aortitis, but significant differences with IgG4-TAA were not identified. Clearly discriminating pathologically between IgG4-TAA and Takayasu aortitis was thus sometimes difficult until identification of the medial necrosis or giant cells seen in Takayasu aortitis.

Infectious aortitis showed thickening of the entire wall and adventitia due to massive infiltration of inflammatory cells and edematous changes. Adventitial thickness was greater in infectious aortitis (mean, 6.0 mm; range, 5.6-7.0 mm) than in IgG4-TAA ( $P = .01$ ). Massive neutrophil infiltration was frequently seen in infectious aortitis and was significantly higher than in IgG4-TAA ( $P = .005$ ).

**Clinical features of IgG4-TAA.** Clinical characteristics of patients with thoracic aortic lesions are summarized in Table III. All IgG4-TAA cases occurred in older men (mean age, 71 years; range, 67-74 years). Age and gender were almost the same in IgG4-related and nonrelated TAA and in infectious aortitis. The male predilection seen in IgG4-TAA differed significantly from the findings for aortic dissection and Takayasu aortitis ( $P = .05$  and  $P = .013$ , respectively). In addition, patients with Takayasu aortitis were significantly younger than those with IgG4-TAA ( $P =$

**Table I.** Clinicopathologic features of patients with immunoglobulin G4 (IgG)-related thoracic aortic lesion

| Pt | Age (years)/<br>sex | Form                                    | Location    | Diameter<br>(cm) | Previous diagnosis            | Medical history                              | Blood test                 |                | Histology                        |                             |
|----|---------------------|-----------------------------------------|-------------|------------------|-------------------------------|----------------------------------------------|----------------------------|----------------|----------------------------------|-----------------------------|
|    |                     |                                         |             |                  |                               |                                              | WBC<br>(/mm <sup>3</sup> ) | CRP<br>(mg/dL) | IgG4+<br>cell<br>counts<br>(hpf) | IgG4+/<br>IgG+<br>cells (%) |
| 1  | 67/M                | Saccular<br>aneurysm                    | Distal arch | 4.2              | Inflammatory<br>aneurysm      | Bronchial asthma;<br>low-grade fever         | 8900                       | 1.2            | 90.3                             | 76.3                        |
| 2  | 74/M                | Fusiform<br>aneurysm                    | Arch        | 7.0              | Lymphoplasmacytic<br>aortitis | Bronchial asthma,<br>allergy, gastric ulcer  | 5600                       | 2.8            | 112.3                            | 85.5                        |
| 3  | 71/M                | Fusiform<br>aneurysm                    | Distal arch | 5.5              | Atherosclerotic<br>aneurysm   | Allergy, rheumatism,<br>hypertension         | 6500                       | 3.5            | 90.3                             | 70.5                        |
| 4  | 76/M                | Saccular<br>aneurysm<br>with<br>rupture | Distal arch | 6.3              | Atherosclerotic<br>aneurysm   | Allergy, hypertension,<br>chronic bronchitis | 6100                       | 8.7            | 127.7                            | 82.9                        |
| 5  | 68/M                | Saccular<br>aneurysm                    | Arch        | 6.1              | Atherosclerotic<br>aneurysm   | Bronchial asthma,<br>hypertension            | 7700                       | 1.1            | 133.3                            | 76.5                        |

CRP, C-reactive protein; WBC, white blood cell count.

**Table II.** Pathologic findings of thoracic aortic lesions

| Variable <sup>a</sup>         | IgG4-TAA<br>(n = 5) | non-IgG4-<br>TAA<br>(n = 66) | P <sup>b</sup> | Aortic<br>dissection<br>(n = 44) | P <sup>b</sup> | Takayasu<br>disease<br>(n = 7) | P <sup>b</sup> | Infectious<br>aortic<br>aneurysm<br>(n = 3) | P <sup>b</sup> |
|-------------------------------|---------------------|------------------------------|----------------|----------------------------------|----------------|--------------------------------|----------------|---------------------------------------------|----------------|
| Aortic wall thickness<br>(mm) | 6.5 ± 1.7           | 4.3 ± 1.5                    | <.05           | 4.3 ± 1.1                        | <.05           | 4.6 ± 2.0                      | ...            | 7.8 ± 1.3                                   | ...            |
| Adventitial thickness<br>(mm) | 4.2 ± 0.7           | 1.4 ± 1.4                    | <.001          | 0.9 ± 1.3                        | <.001          | 2.2 ± 1.5                      | <.05           | 6.2 ± 0.7                                   | <.05           |
| Intimal thickness<br>(mm)     | 2.7 ± 0.8           | 2.6 ± 0.9                    | ...            | 0.8 ± 1.1                        | <.05           | 1.3 ± 1.0                      | <.05           | 2.8 ± 0.3                                   | ...            |
| Plasma cells, >10/hpf         | 5 (100)             | 48 (73)                      | ...            | 12 (27)                          | <.001          | 6 (86)                         | ...            | 3 (100)                                     | ...            |
| Eosinophils, >5/hpf           | 3 (60)              | 1 (2)                        | <.001          | 1 (2)                            | <.001          | 0                              | <.05           | 1 (33)                                      | ...            |
| Neutrophils, >10/hpf          | 0                   | 22 (33)                      | ...            | 3 (100)                          | <.05           | ...                            | ...            | ...                                         | ...            |
| Lymphoid follicles            | 5 (100)             | 24 (36)                      | <.05           | 9 (21)                           | <.05           | 4 (57)                         | ...            | 1 (33)                                      | <.05           |
| Obliterative phlebitis        | 4 (80)              | 6 (9)                        | <.001          | 1 (2)                            | <.001          | 0                              | ...            | ...                                         | ...            |
| Perineural<br>inflammation    | 5 (100)             | 10 (15)                      | <.001          | 1 (2)                            | <.001          | 0                              | <.05           | 0                                           | <.05           |
| Medial necrosis               | 0                   | 0                            | ...            | 2 (67)                           | <.05           | ...                            | ...            | ...                                         | ...            |
| Granuloma                     | 0                   | 0                            | ...            | 4 (10)                           | ...            | 6 (86)                         | <.05           | 1 (33)                                      | ...            |
| Giant cell                    | 0                   | 10 (15)                      | ...            | 31 (7)                           | <.05           | 2 (29)                         | ...            | 0                                           | ...            |
| IgG4+ cells (hpf)             | 110.8 ± 20.2        | 15.4 ± 22.1                  | <.001          | 14.0 ± 27.0                      | <.001          | 12.1 ± 9.8                     | <.001          | 27.1 ± 19.3                                 | <.001          |
| IgG4+/IgG+ cells<br>(%)       | 77.4 ± 7.7          | 11.6 ± 17.9                  | <.001          | 3.0 ± 8.4                        | <.001          | 2.8 ± 4.0                      | <.001          | 17.3 ± 16.6                                 | <.001          |

IgG, Immunoglobulin G; TAA, thoracic aortic aneurysm.

<sup>a</sup>Continuous data are presented as mean ± SD; categorical data as No. (%).<sup>b</sup>P means that each subgroup compared with IgG4-TAA.

.009); indeed, no cases of Takayasu aortitis were seen in patients aged >65. Peripheral adhesion due to fibrous and inflammatory change of adventitia was significantly more frequently detected in IgG4-TAA than non-IgG4-TAA and aortic dissection ( $P < .001$  each).

Interestingly, all cases of IgG4-TAA occurred in the aortic arch, particularly in the distal arch, whereas only 32% of non-IgG4-TAA ( $P = .002$ ), 16% of aortic dissections ( $P = .002$ ), and no cases of Takayasu aortitis ( $P = .01$ ) or infectious aortitis involved the aortic arch ( $P = .001$ ). Aneurysmal diameters were equivalent between IgG4-

TAA, non-IgG4-TAA, and Takayasu disease. The saccular form was significantly more frequent in IgG4-TAA (3 cases, 60%) than in non-IgG4-TAA (3 patients, 18%;  $P = .027$ ) or Takayasu disease (0%;  $P = .018$ ; Fig 4).

The incidence of aneurysm rupture was basically the same in all groups. No patients with IgG4-TAA died intraoperatively or  $\leq 30$  days after surgery.

**Medical history.** Patients with IgG4-TAA had no medical history of autoimmune pancreatitis and showed no tumorous involvement of IgG4-SD in other organs on radiologic examination during follow-up. Bronchial asthma was

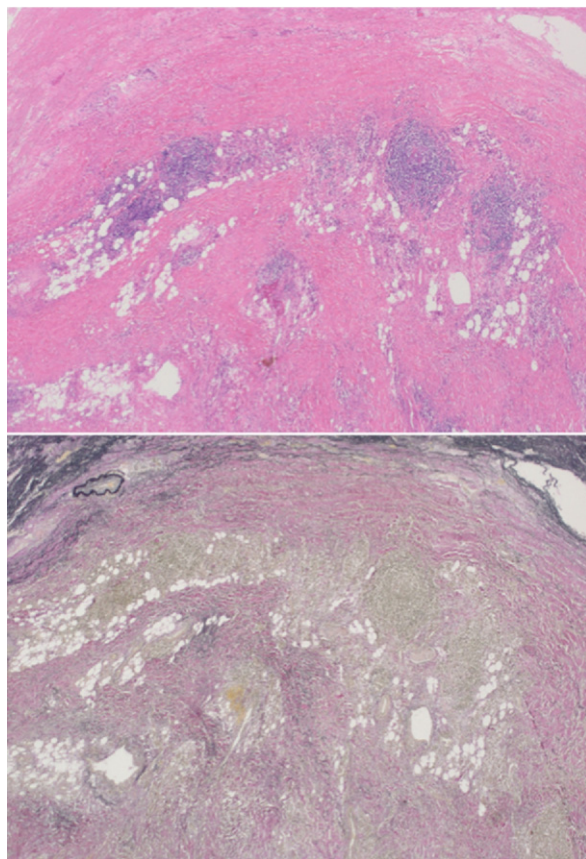


**Fig 3.** Histopathologic features of IgG4-related thoracic aortic aneurysm in patient 3. Thickened fibrotic media to adventitia shows loss of elastic tissue and muscles and inflammatory cell infiltration mainly in the adventitia of the aortic wall. Fibrous tissue extends into adjacent adventitial fat. **Upper panel,** Hematoxylin and eosin. **Lower panel,** elastica van Gieson (both images, original magnification  $\times 20$ , in almost the same field).

more often detected in IgG4-TAA (3 patients, 60%) than in non-IgG4-TAA ( $P < .001$ ), aortic dissection ( $P < .001$ ), or Takayasu aortitis ( $P = .018$ ). Patient 5, with IgG4-TAA and bronchial asthma, had been treated by low-dose corticosteroid administration, whereas the others had not been medicated by corticosteroids. Details of medications for 2 non-IgG4-TAA patients with bronchial asthma were unavailable. Allergies (to drugs, contrast medium, spices, etc) were also more frequent in IgG4-TAA than in non-IgG4-TAA ( $P = .025$ ), aortic dissection ( $P = .005$ ), or Takayasu aortitis ( $P = .018$ ). Only patient 3, with IgG4-TAA, showed rheumatism. Two patients with non-IgG4-TAA showed systemic connective tissue disease (systemic lupus erythematosus and rheumatism). These patients with autoimmune disease did not have systemic aortitis. No significant difference in incidence of autoimmune diseases was seen between subgroups. Smoking habits and hypertension were often detected in all subgroups of thoracic lesions.

**Laboratory findings.** Serum levels of WBC and CRP were higher in IgG4-TAA ( $P = .025$ ) than in non-IgG4-TAA ( $P = .045$ ). IgG4 was examined in patient 5, with IgG4-TAA, who had a high serum IgG4 concentration (185 mg/dL; normal,  $<135$  mg/dL). This patient also had a high serum IgE concentration (335 IU/mL, normal,  $<170$  IU/mL) and positive results for antinuclear antibody (sp80). The serum IgG4 level in this patient normalized after TAA resection. Leukocytosis and elevated CRP concentrations were also detected in Takayasu aortitis and infectious aortitis, with no significant differences between IgG4-TAA and these diseases.

## DISCUSSION

This study examined the clinicopathologic features of IgG4-SD in the thoracic aorta. The main results can be summarized as follows:

1. IgG4-SD can occur in the thoracic aorta in an aneurysmal shape; among our five patients with IgG4-TAA were one with lymphoplasmacytic aortitis, one with inflammatory aneurysm, and three with atherosclerotic aneurysm; thus, IgG4-TAA comprised 7% of TAAs and 4% of all thoracic aortic lesions;
2. IgG4-TAA showed histologic features similar to other IgG4-SD;
3. IgG4-TAA displayed similar clinical features to IgG4-related inflammatory AAA, with a predilection for older men, medical history of bronchial asthma and allergy, serologic leukocytoclasia, and elevated CRP concentrations; and
4. characteristic involvement of the aortic arch, saccular form, and fibrous adhesion to surrounding tissue.

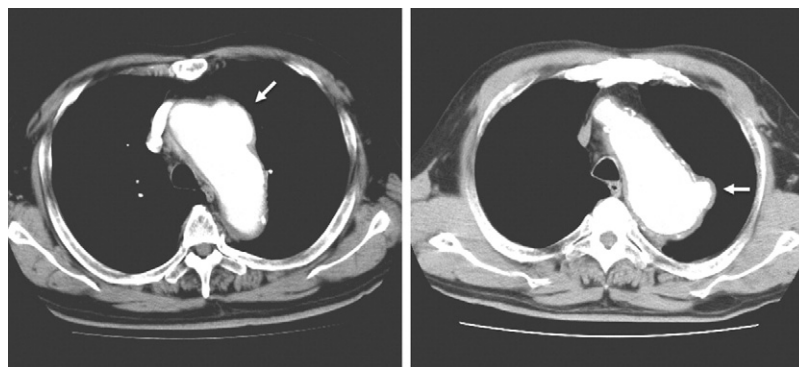
We confirmed that IgG4-TAA showed similar histopathologic characteristics to other IgG4-SD,<sup>7,23,24</sup> particularly to IgG4-related inflammatory AAA.<sup>14,15</sup> That is, IgG4-TAA was characterized by diffuse lymphoplasmacytic infiltration, irregular fibrosis, obliterative phlebitis, and frequent eosinophilic infiltration. Immunostaining for IgG4 revealed diffuse infiltration of IgG4-positive plasmacytes. In addition, thicker entire aortic wall and adventitia seen in IgG4-TAA resembled that of IgG4-related inflammatory AAA.<sup>14,15</sup> IgG4-TAA did not show granulomas, medial degeneration, medial laminar necrosis or neutrophil infiltration.

IgG4-related inflammatory AAA comprised 40% of inflammatory AAAs and 5% of total AAAs.<sup>15</sup> Similarly, we found five patients with IgG4-TAA, representing 7% of TAAs and 4% of all thoracic aortic lesions. The incidence of IgG4-SD at the thoracic aorta appears almost equal to that of the abdominal aorta and is not particularly rare.<sup>25</sup> On top of the predilection in older men, we determined that the location in the aortic arch and frequent saccular form was clinically characteristic for IgG4-TAA, in contrast to non-IgG4-TAA.<sup>23</sup> Considering the dramatic response of patients with IgG4-SD to steroid therapy,<sup>23</sup> the possibility of using steroids for IgG4-TAA is an interesting issue. However, steroid therapy may increase the risk of rupture by

**Table III.** Clinical findings of thoracic aortic lesions

| Variable <sup>a</sup>                    | IgG4-TAA<br>(n = 5) | non-IgG4-TAA<br>(n = 66) | P <sup>b</sup> | Aortic<br>dissection<br>(n = 44) | P <sup>b</sup> | Takayasu<br>disease<br>(n = 7) | P <sup>b</sup> | Infectious aortic<br>aneurysm<br>(n = 3) | P <sup>b</sup> |
|------------------------------------------|---------------------|--------------------------|----------------|----------------------------------|----------------|--------------------------------|----------------|------------------------------------------|----------------|
| Age (years)                              | 71.2 ± 3.8          | 70.6 ± 9.4               |                | 62.5 ± 10.9                      |                | 47.1 ± 16.3                    | <.05           | 75.0 ± 6.1                               |                |
| Gender                                   |                     |                          | ...            |                                  | <.05           |                                | <.05           |                                          | ...            |
| Male                                     | 5                   | 32                       |                | 24                               |                | 2                              |                | 3                                        |                |
| Female                                   | 0                   | 34                       |                | 20                               |                | 5                              |                | 0                                        |                |
| Location, No.                            |                     |                          | ...            |                                  |                |                                | ...            |                                          | ...            |
| Ascending aorta                          | 0                   | 30                       |                | 26                               |                | 5                              |                | 0                                        |                |
| Arch                                     | 5                   | 21                       |                | 7                                |                | 0                              |                | 0                                        |                |
| Descending aorta                         | 0                   | 15                       |                | 11                               |                | 2                              |                | 3                                        |                |
| Location, arch                           | 5 (100)             | 21 (32)                  | <.05           | 7 (16)                           | <.05           | 0                              | <.05           | 0                                        | <.05           |
| Aneurysmal<br>diameter (cm)              | 6.3 ± 0.6           | 6.4 ± 1.9                | ...            | ...                              | ...            | 5.7 ± 2.5 <sup>c</sup>         | ...            | 4.0 ± 3.0                                | <.05           |
| Rupture                                  | 1 (20)              | 16 (24)                  | ...            | ...                              | ...            | 0                              | ...            | 2 (67)                                   | ...            |
| Saccular form                            | 3 (60)              | 12 (18)                  | <.05           | ...                              | ...            | 0                              | <.05           | 1 (33)                                   | ...            |
| Peripheral adhesion                      | 4 (80)              | 8 (12)                   | <.001          | 2 (5)                            | <.001          | 0                              | <.001          | 3 (100)                                  | ...            |
| Aneurysms in other<br>locations          | 1 (20)              | 18 (27)                  | ...            | 3 (7)                            | <.05           | 4 (57)                         | ...            | 1 (33)                                   | ...            |
| Autoimmune disease                       | 1 (20)              | 2 (3)                    | ...            | 3 (7)                            | ...            | 0                              | ...            | 0                                        | ...            |
| Bronchial asthma                         | 3 (60)              | 2 (3)                    | <.001          | 2 (5)                            | <.001          | 0                              | <.05           | 2 (67)                                   | ...            |
| Allergy                                  | 3 (60)              | 7 (11)                   | <.05           | 5 (11)                           | <.05           | 0                              | <.05           | 1 (33)                                   | ...            |
| White blood cells<br>(/mm <sup>3</sup> ) | 7800 ± 1500         | 4900 ± 2700              | <.05           | ...                              | ...            | 6700 ± 1800                    | ...            | 11400 ± 3300                             | <.05           |
| C-reactive protein<br>(mg/dL)            | 2.9 ± 3.4           | 0.9 ± 2.7                | <.05           | ...                              | ...            | 2.4 ± 1.4                      | ...            | 7.3 ± 2.1                                | <.05           |

IgG, Immunoglobulin G; TAA, thoracic aortic aneurysm.

<sup>a</sup>Continuous data are presented as the mean ± standard deviation; categoric data as No. (%).<sup>b</sup>P means that each subgroup compares with IgG4-TAA.<sup>c</sup>4 patients.**Fig 4.** Axial contrast-enhanced computed tomography of immunoglobulin G4-related thoracic aortic aneurysm in (Left) patient 4, and (Right) patient 5. Both patients showed irregular thickness of the aortic wall with homogeneous enhancement and several central calcifications of the aortic wall. Saccular-shaped aneurysm of aortic arch was seen in patient 4. Patient 5 shows dilatation of the aortic arch to descending aorta with an oval bulge in the portion of the distal aortic arch (arrow).

making the wall thinner. The present study cannot provide any data about this issue, and further clinical investigation seems mandatory.

We have previously reported significantly higher serum IgG4 and IgE concentrations in IgG4-related inflammatory AAA.<sup>15</sup> In addition, high titers of antinuclear antibody were more commonly observed in such patients.<sup>15</sup> Only one of the IgG4-related cases had high serum concentra-

tions of IgG4 and IgE in the present study. We were unable to identify the serologic characteristics of IgG4-TAA in the present small series, but high serum IgG4 and IgE concentrations and the presence of antinuclear antibody might represent useful laboratory signs in screening for IgG4-SD.<sup>15</sup>

Interestingly, three patients (60%) with IgG4-TAA had histories of bronchial asthma. Similarly, our previous study revealed that 31% of patients with IgG4-related inflamma-

tory AAA had a medical history of bronchial asthma.<sup>15</sup> Although the direct relationship between bronchial asthma and IgG4-SD has not yet been elucidated, bronchial asthma has been reported as one manifestation of IgG4-SD.<sup>23</sup> We speculate that an allergic predisposition is important for the development of IgG4-SD. Indeed, three patients (60%) with IgG4-TAA had an allergy, similar to patients with IgG4-related inflammatory AAA.<sup>15</sup> More importantly, IgG4-SD is immunologically characterized by a Th2-predominant immune reaction and activation of regulatory T-cells. Such immune reactions resemble allergic disorders.<sup>26</sup>

No standard diagnostic criteria have been set for inflammatory aneurysm.<sup>10-12</sup> Thus, "inflammatory TAA" is considered to be a vague and rarely reported entity, in contrast with inflammatory AAA.<sup>27-40</sup> Indeed, patient 1 (0.8%), with inflammatory TAA with thicker adventitia (>5 mm), met our criteria for IgG4-SD. IgG4-related inflammatory TAA has also been reported more recently,<sup>21</sup> and that case was consistent with our findings for IgG4-TAA. Moreover, we paid attention to previous reports of three cases of inflammatory TAA that certainly resembled IgG4-TAA in this series, including adult men, location of the ascending aorta to aortic arch, and complications of retroperitoneal or mediastinal fibrosis.<sup>27,38,40</sup> Inflammatory AAA has been considered to be part of the family of disorders often referred to as "chronic periaortitis."<sup>41,42</sup> Recently, IgG4-related inflammatory AAA could be estimated as IgG4-related chronic periaortitis together with retroperitoneal fibrosis.<sup>14,15,20,43</sup> We therefore emphasize that IgG4-related chronic periaortitis could be expanded to include IgG4-TAA and IgG4-related mediastinal fibrosis.

In the thoracic aorta, several etiologic agents have been suggested for the development of aneurysms with aortitis. No distinct clinical examination or laboratory test permits differentiation between IgG4-TAA and aneurysmal-shaped Takayasu aortitis,<sup>18,25</sup> except for the age range, gender, and serum IgG4 concentration. Histologically, Takayasu aortitis has a relatively thicker aortic wall<sup>19</sup>; however, the adventitia in IgG4-TAA was significantly thicker than that of Takayasu aortitis. Although the present series did not include thoracic lesions of isolated aortitis, we were less concerned with IgG4-SD and isolated aortitis because adventitial inflammation and fibrous thickening of isolated aortitis were minimal.<sup>9</sup>

Aortic dissection and aortic aneurysm are considered to have different natural histories, pathogenesis, and etiologies.<sup>18,25</sup> Pathologically, however, old and healing dissections would show periaortitis due to reactive changes, either inflammatory granulation tissue or dense fibrosis from the media to the adventitia.<sup>18</sup> Indeed, in the present study, five patients (11%) with aortic dissection showed periaortic fibrosis with inflammatory changes. Interestingly, Stone et al<sup>22</sup> recently reported a patient with aortic dissection associated with IgG4-SD (lymphadenitis), suggesting that lymphoplasmacytic aortitis due to IgG4-SD could cause aortic dissection, whereas we did not find aortic dissection with IgG4-SD. This case thus have important

implications regarding the possible forms of IgG4-SD involving the thoracic aorta.

## CONCLUSIONS

The present study revealed that IgG4-SD can occur in the thoracic aorta as an aneurysmal shape, including lymphoplasmacytic aortitis and inflammatory aneurysm. Patients with IgG4-TAA showed similar clinicopathologic characteristics to those with other IgG4-SD. In addition, involvement of the aortic arch, sacular form, and fibrous adhesion are characteristic of IgG4-TAA. Our findings indicated that IgG4-SD, as IgG4-related chronic periaortitis, should be considered in patients with thoracic aortic lesions of unknown cause.

## AUTHOR CONTRIBUTIONS

Conception and design: SK, YZ  
Analysis and interpretation: SK, YZ, AZ  
Data collection: SK, ME, YM, FK, HO  
Writing the article: SK, YZ  
Critical revision of the article: SK  
Final approval of the article: SK, AK, YM  
Statistical analysis: SK  
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Overall responsibility: SK

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