

Inflammatory Abdominal Aortic Aneurysm: Close Relationship to IgG4-related Periaortitis

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Abstract: Inflammatory abdominal aortic aneurysm (AAA) is a member of a family of disorders referred to as “chronic periaortitis” together with retroperitoneal fibrosis. Retroperitoneal fibrosis is included in IgG4-related disease, which is characterized by numerous infiltrating IgG4-positive plasma cells and high serum IgG4 concentrations. However, the relationship between IgG4-related disease and inflammatory AAA has not been documented. In this study, we examined the clinicopathologic characteristics of inflammatory (10 cases) and atherosclerotic (22 cases) AAAs, based on the hypothesis that inflammatory AAA might be related to IgG4-related disease. Cases of inflammatory AAA could be classified into 2 groups based on immunostaining of IgG4. Four patients showed diffuse infiltration of abundant IgG4-positive plasma cells (IgG4-related cases), whereas the remaining 6 cases of inflammatory AAA and all cases of atherosclerotic AAA had only a few IgG4-positive plasma cells (non-IgG4-related cases). IgG4-related inflammatory AAA was pathologically characterized by the frequent infiltration of eosinophils, lymph follicle formation, perineural inflammatory extension, and inconspicuous infiltration of neutrophils compared with non-IgG4-related inflammatory AAA. Obliterative phlebitis, which is venous occlusion with inflammatory cell infiltration, is observed in all IgG4-related cases. In addition, serum IgG4 concentrations were significantly higher in IgG4-related inflammatory AAA (109 to 559 mg/dL, normal range: 4 to 110 mg/dL) than non-IgG4-related inflammatory AAA (32 to 59 mg/dL) and all atherosclerotic AAA (12 to 83 mg/dL). In conclusion, inflammatory AAAs might be classified into 2 groups: IgG4-related or nonrelated. The former might be one of the IgG4-related diseases, and could be included in IgG4-related periaortitis together with retroperitoneal fibrosis.

Key Words: IgG4, autoimmune pancreatitis, retroperitoneal fibrosis, aneurysm, inflammation

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Abdominal aortic aneurysm (AAA) is the most common type of aneurysm, developing in 4% to 10% of people older than 60 years.^{6,20} Although AAA has been recognized for centuries, the unique variant, inflammatory AAA, was not described until 1972. Walker et al²⁷ first reported that 10% of 187 patients with AAA demonstrated the characteristic features of the inflammatory variant: marked thickening of the aneurysm wall, fibrosis of the adjacent retroperitoneum, and rigid adherence of the adjacent structures to the anterior aneurysm wall. Several hypotheses like autoimmune reactions, infections of *Chlamydia pneumoniae*, and lipid oxidation have been suggested to explain its pathogenesis, but the etiology of inflammatory AAA is still unknown.^{11,19,23,24,26}

The relationship between IgG4 and sclerosing diseases was first reported with regard to autoimmune pancreatitis in 2001.² Hamano et al² reported that patients with autoimmune pancreatitis have a high serum IgG4 concentration. Autoimmune pancreatitis is pathologically called lymphoplasmacytic sclerosing pancreatitis, which is characterized by diffuse lymphoplasmacytic infiltration, acinar atrophy, occasional eosinophilic infiltration, and obliterative phlebitis.¹² In addition, immunostaining of IgG4 revealed abundant IgG4-positive plasma cells diffusely distributed in patients with pancreatitis.^{1,33} Until this time, similar sclerosing lesions had been identified in the bile duct (sclerosing cholangitis),²⁹ salivary gland (chronic sclerosing sialadenitis),¹³ and retroperitoneum (retroperitoneal fibrosis).^{3,31} Those sclerosing lesions have clinicopathologic features similar to autoimmune pancreatitis, and are now estimated to belong to a disease entity named *IgG4-related disease*.¹⁰

IgG4 is the rarest of the IgG subclasses to be expressed, accounting for only 3% to 6% of all the IgG in normal serum. IgG4 can induce the migration of leukocytes, but does not bind to complement. High serum

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IgG4 concentrations are only found in a limited number of conditions including atopic dermatitis, bronchial asthma, pemphigus vulgaris, and pemphigus foliaceus.^{5,22} IgG4-related disease is a unique sclerosing disorder involving elevated levels of IgG4.

IgG4-related diseases have not been reported in the cardiovascular system until now. Interestingly, we previously found a case of retroperitoneal and mediastinal fibrosis with a mass surrounding the aorta from the aortic arch to the bifurcation of the aorta.³¹ The patient did not have an aneurysm, although we speculated that IgG4-related inflammation occurring in the retroperitoneum or periaortic tissue might cause AAA, especially inflammatory AAA, in other patients.

In this study, we examined pathologic characteristics of inflammatory and atherosclerotic AAAs with special reference to IgG4-positive plasma cell infiltration. In addition, we examined serum IgG4 concentrations of patients. This study revealed that a subgroup of inflammatory AAA has clinicopathologic characteristics similar to IgG4-related disease.

MATERIALS AND METHODS

Case Selection

This study consisted of 10 cases of inflammatory AAA and 22 cases of noninflammatory atherosclerotic AAA. All cases were surgically treated in Kanazawa University Hospital or Kanazawa Medical Center, Kanazawa, Japan. Cases of inflammatory AAA were prospectively and retrospectively collected from the files of the Pathology Departments from 1992 to 2006. All cases of atherosclerotic AAA were prospectively collected for 2 years (2005 and 2006). The age and sex of the patients were as follows: inflammatory AAA, 58 to 81 (mean age 71) years, 9 males and 1 female; atherosclerotic AAA, 59 to 89 (mean age 77) years, 17 males

and 5 females. Aneurysms were localized to within the abdominal aorta in all the cases of inflammatory AAA except one, in which there was both AAA and a right iliac aneurysm. Similarly, 19 out of 22 atherosclerotic AAAs were located in the abdominal aorta, whereas the remaining 3 patients had a right iliac aneurysm (2 cases) and thoracic aorta aneurysm (1 case) in addition to AAA. None of the patients with inflammatory AAA had a history of rupture, whereas 3 patients with atherosclerotic AAA were surgically treated just after an aneurysmal rupture. All patients underwent graft replacement surgical procedures. No patients had any history of extra-retroperitoneal IgG4-related diseases like autoimmune pancreatitis or chronic sclerosing sialadenitis.

Inflammatory AAA was clinicopathologically diagnosed.²⁷ During surgery, the surgeons identified diffuse thickening of the aneurysm wall and fibrous adhesion between the aneurysm and the retroperitoneum in 7 of 10 cases of inflammatory AAA. The remaining 3 patients showed mild adhesion to the retroperitoneum. The histologic characteristics of inflammatory AAA are described in the results section (Table 1).

Laboratory Data

Preoperative serum samples were available in 6 of 10 cases of inflammatory AAA and all cases of atherosclerotic AAA. Serum concentrations of IgG, IgA, IgM, and IgG4, and antinuclear antibodies (ANA) were analyzed. The serum IgG4 concentration was measured by nephelometry.

Histologic Evaluation

Tissue samples from each surgically resected specimens were fixed in neutral formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin and elastica-van Gieson (EvG). The rest were used for immunohistochemistry.

TABLE 1. Comparison of Histologic Features Between Inflammatory and Atherosclerotic AAAs and Between IgG4-related and Nonrelated Inflammatory AAAs

	Atherosclerotic AAA (n = 22)	Inflammatory AAA (n = 10)	P	Inflammatory AAA		P
				IgG4-related (n = 4)	Non-IgG4-related (n = 6)	
Thickness of the adventitia (mm)*	0.7 (0.1-5.0)	5.5 (2.5-8.6)	< 0.001	5.6 (3.4-8.6)	5.4 (2.5-7.2)	0.915
Degree of inflammation (3+, 2+, 1+, 0)†	0/2/16/4	7/3/0/0	< 0.001	4/0/0/0	3/3/0/0	0.109
Neutrophils (> 10/hpf)	17 (77%)	4 (40%)	0.043	0	4 (66.7%)	0.046
Eosinophils (> 5/hpf)	0	7 (70%)	< 0.001	3 (75%)	0	0.016
Plasma cells (> 10/hpf)	8 (36%)	10 (100%)	< 0.001	4 (100%)	6 (100%)	Identical
Lymph follicle with germinal center	2 (9%)	5 (50%)	0.011	4 (100%)	1 (17%)	0.014
Obliterative phlebitis	0	7 (70%)	< 0.001	4 (100%)	3 (50%)	0.109
Granuloma formation	1 (5%)	2 (20%)	0.171	1 (25%)	1 (17%)	0.759
Perineural inflammatory extension	0	60 (60%)	< 0.001	4 (100%)	2 (33%)	0.046

*Data are shown as average (range).

†Definition of each grade is mentioned in the Materials and Methods section.

We histologically examined the degree of inflammation in the adventitia (0, minimal inflammatory cell infiltration; 1+, focal accumulation of inflammatory cells; 2+, between 1+ and 3+; and 3+, diffuse inflammatory cell infiltration). We also examined whether the following 7 histologic features were evident: neutrophilic infiltration [more than 10 per high-power field (hpf)], eosinophilic infiltration (more than 5/hpf), plasma cell infiltration (more than 10/hpf), lymph follicle with germinal center, obliterative phlebitis, granuloma formation, and perineural inflammatory cell infiltration. We examined those features in more than 30 fields in each case. A positive case was defined as having each finding in at least 1 field. The adventitial thickness (from the lowest elastic fiber of the media to the lowest part of the adventitia) in each case was calculated on EvG-stained sections using a microscopic measure.

Immunohistochemistry for IgG and IgG4

Immunostaining of IgG and IgG4 was performed by an autostainer (HX System Benchmark, Ventana Medical Systems, Tucson, AZ) as per the manufacturer's instructions. Primary antibodies used were a rabbit monoclonal antibody against human IgG (Dako Cytomation, Glostrup, Denmark) and a mouse monoclonal antibody for human IgG4 (ZYMED Laboratory, Inc, San Francisco, CA). 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 plasma cells were counted in 5 different hpf (10× eyepiece and 40× lens) in the more prominently inflamed areas in the aneurysm wall, and the numbers were compared. The ratio of IgG4-positive cells to IgG-positive cells was also calculated in each case.

Statistics

Means of 2 groups were compared with the Mann-Whitney *U* test. Values of $P < 0.05$ were regarded as significant.

RESULTS

Histologic Characteristics of Inflammatory AAA

We have summarized the histologic characteristics of inflammatory AAA in Table 1. The aneurysm wall exhibited diffuse fibrous thickening of the aortic wall. Inflammatory AAA showed marked enlargement of the adventitia (Fig. 1). The adventitia was significantly thicker in inflammatory AAA than atherosclerotic AAA ($P < 0.001$). Inflammatory cell infiltration was diffusely observed in the adventitia, and was more severe in inflammatory AAA than atherosclerotic AAA. In inflammatory AAA, lymphocytes and plasma cells diffusely infiltrated intermixed with irregular fibrotic areas. Sclerosing inflammation disrupted elastic fibers in the media. Lymphoid follicles with germinal centers were also present in 5 cases. Many plasma cells were observed in

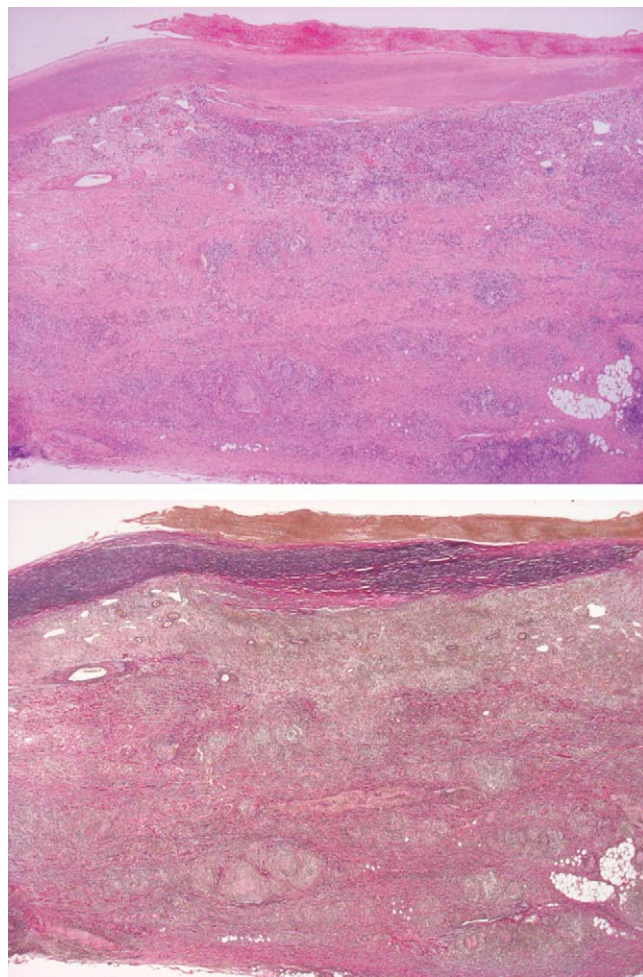


FIGURE 1. Histopathology of inflammatory AAA (an IgG4-related case). The adventitia is severely expanded by irregular fibrous and inflammatory cell infiltration. Upper: hematoxylin and eosin (H&E); lower: EvG; both images: ×200 at almost the same field.

sclerosed areas and between lymphoid follicles. Intimal atherosclerotic changes were observed in both inflammatory and atherosclerotic AAAs. However, atherosclerotic AAA was more commonly associated with erosive and exudative changes, and also had neutrophilic infiltration in the intima and media (Table 1). In contrast, 7 cases (70%) of inflammatory AAA had conspicuous eosinophilic infiltration (more than 5/hpf) (Fig. 2; Table 1). Interestingly, obliterative phlebitis could be identified in the adventitia of inflammatory aneurysms by using EvG staining (Fig. 2). In addition, lymphoplasmacytic infiltration commonly extended along nerve fascicles in inflammatory AAA (Fig. 2).

Immunostaining of IgG and IgG4 in AAA

Immunostaining of IgG revealed many IgG-positive plasma cells in the adventitia of all inflammatory AAAs (Fig. 3). The cases of atherosclerotic AAA with mild

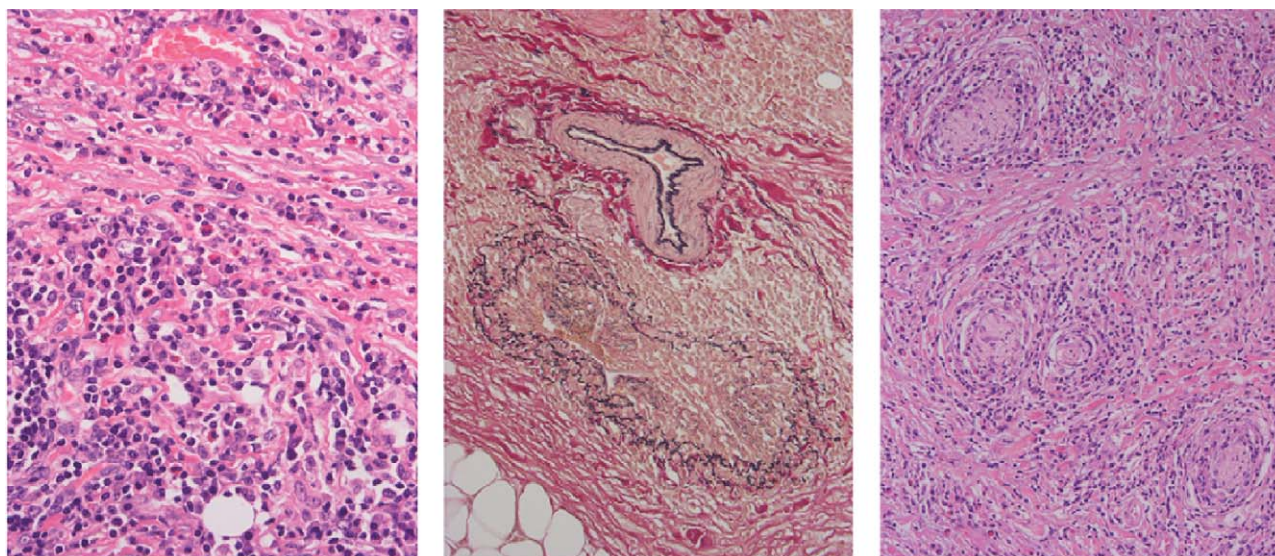


FIGURE 2. Histopathology of inflammatory AAA (an IgG4-related case). Many plasma cells and eosinophils are observed in an inflamed area (left, H&E, $\times 400$). Obliterative phlebitis is observed in the adventitia (middle, EvG, $\times 200$). Inflammatory cells infiltrate along nerve fascicles (right, H&E, $\times 200$).

lymphoplasmacytic inflammation also showed several IgG-positive plasma cells in the aneurysm walls. The numbers of IgG-positive plasma cells were significantly higher in inflammatory AAA ($126.1 \pm 55.8/\text{hpf}$) than atherosclerotic AAA ($20.3 \pm 26.4/\text{hpf}$) ($P < 0.001$) (Fig. 4). In addition, IgG4-positive plasma cells were more numerous in inflammatory AAA ($48.5 \pm 61.9/\text{hpf}$) than atherosclerotic AAA ($1.2 \pm 1.5/\text{hpf}$) ($P < 0.001$) (Figs. 3, 4). Notably, 4 patients with inflammatory AAA showed a diffuse infiltration of IgG4-positive plasma cells ($114.1 \pm 44.2/\text{hpf}$) (Fig. 3). In contrast, IgG4-positive plasma cells were few or only focally accumulated in the remaining 6 cases of inflammatory AAA ($5.2 \pm 2.2/\text{hpf}$) and all cases of atherosclerotic AAA ($1.2 \pm 1.5/\text{hpf}$) (Fig. 3). No IgG4-positive plasma cells could be identified in 8 cases of atherosclerotic AAA. The ratios of IgG4/IgG-positive plasma cells were significantly higher in inflammatory AAA ($29.7 \pm 32.4\%$) than atherosclerotic AAA ($3.4 \pm 4.1\%$) ($P = 0.008$) (Fig. 4).

Subclassification of Inflammatory AAA

On the basis of the results of immunostaining of IgG and IgG4, inflammatory AAA could be classified into cases with or without numerous infiltrating IgG4-positive plasma cells. The former is designated IgG4-related inflammatory AAA (4 cases), and the latter as non-IgG4-related inflammatory AAA (6 cases) in this paper. Age and sex did not differ between IgG4-related and non-IgG4-related inflammatory AAA (IgG4-related, 58 to 72 y, 3 males and 1 female; non-IgG4-related, 59 to 81 y, all males).

Next, we examined the pathologic differences between IgG4-related and nonrelated inflammatory AAA (Table 1). The thickness of the adventitia and degree of inflammation did not differ between IgG4-

related and nonrelated inflammatory AAA. IgG4-related inflammatory AAA was pathologically characterized by the frequent infiltration of eosinophils, lymph follicle formation, perineural inflammatory extension, and inconspicuous infiltration of neutrophils compared with non-IgG4-related inflammatory AAA (Fig. 2; Table 1). In addition, obliterative phlebitis was more commonly observed in IgG4-related aneurysms (all cases) than in non-IgG4-related cases (50% of cases), although the difference was not significant (Fig. 2). The number of IgG4-positive cells and the ratio of IgG4/IgG-positive cells were significantly higher in IgG4-related inflammatory AAA, although the numbers of IgG-positive cells were not different in inflammatory AAA irrespective of IgG4-positive plasma cell infiltration (Figs. 3, 4).

Serologic Examination

Preoperative serum samples were available in 3 cases of IgG4-related inflammatory AAA, 3 cases of non-IgG4-related inflammatory AAA, and all cases of conventional AAA. Serum concentrations of IgG, IgA, IgM, and IgG4 are shown in Table 2. Serum levels of IgG, IgA, and IgM did not differ among the 3 groups. Serum IgG concentrations were elevated in 7 cases (1 case of IgG4-related inflammatory AAA and 6 cases of atherosclerotic AAA) (Fig. 5). Interestingly, the serum IgG4 concentration was elevated in 2 cases, both of which were IgG4-related inflammatory AAA. The remaining case of IgG4-related inflammatory AAA showed 109 mg/dL of serum IgG4, which is the upper limit of the normal range (4 to 110 mg/dL). The serum IgG4 level was significantly higher in patients with IgG4-related inflammatory AAA than those with non-IgG4-related inflammatory AAA and atherosclerotic AAA (Fig. 5). ANA was detected in a total of 13 cases. The incidence of ANA did not differ

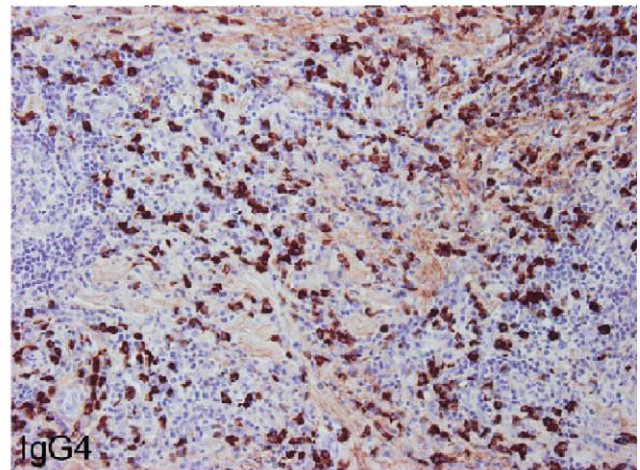
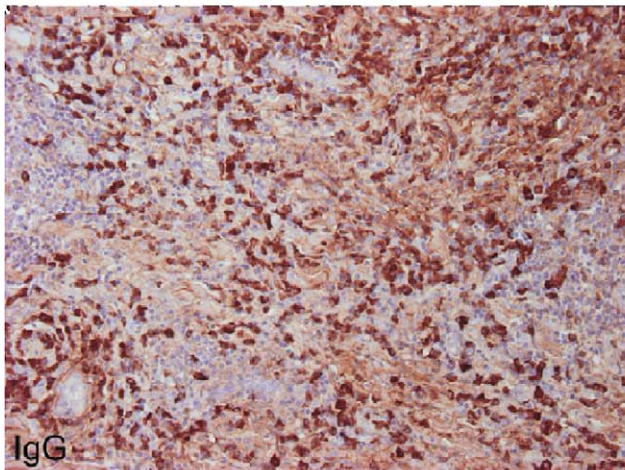
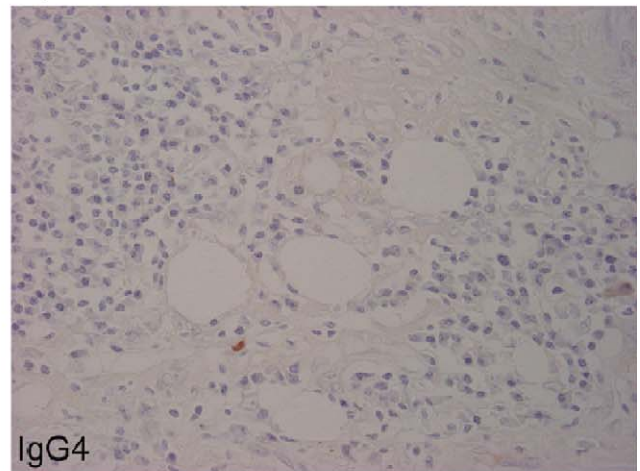
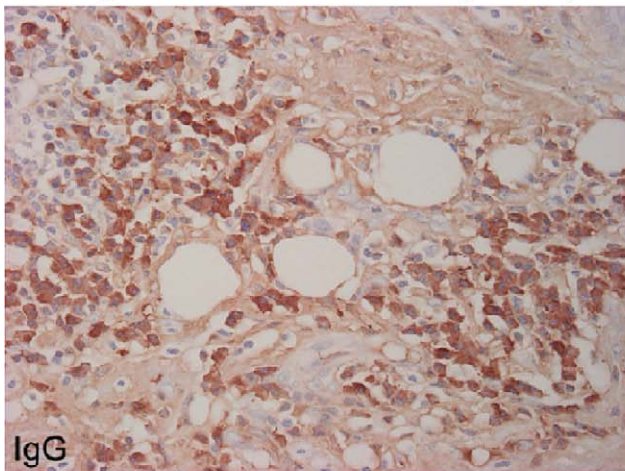
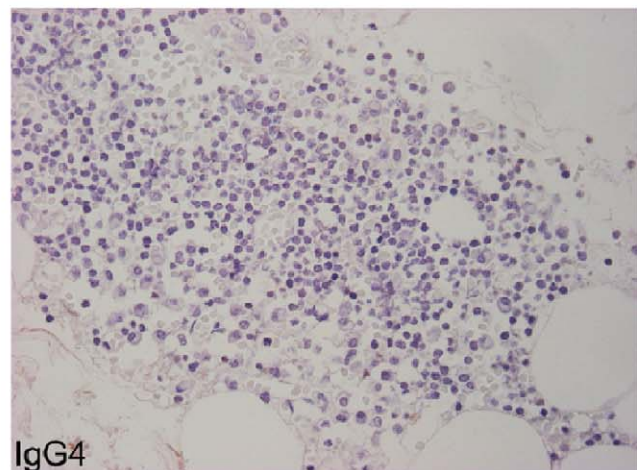
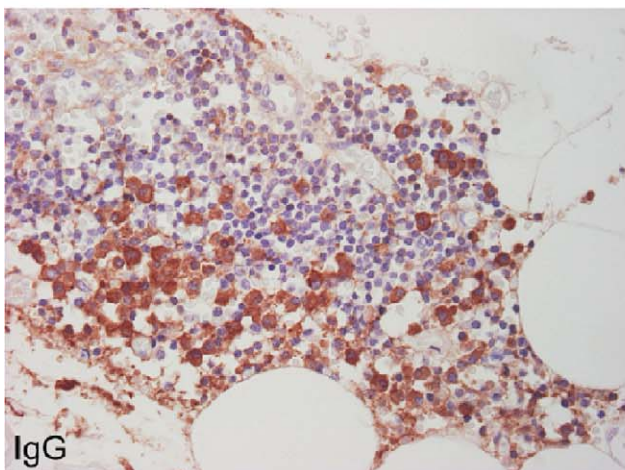
IgG4-related inflammatory AAA (4 cases)**Non IgG4-related inflammatory AAA (6 cases)****Atherosclerotic AAA**

FIGURE 3. Immunohistochemistry of IgG and IgG4 in inflammatory and atherosclerotic AAAs. Many IgG-positive plasma cells are observed in the adventitia of inflammatory AAA. IgG-positive plasma cells are focally accumulated in atherosclerotic AAA. Immunostaining of IgG4 reveals diffuse infiltration of IgG4-positive plasma cells in 4 cases of inflammatory AAA (IgG4-related inflammatory AAA). In contrast, IgG4-positive plasma cells are few in number in the remaining inflammatory AAAs (non-IgG4-related inflammatory AAA) and atherosclerotic AAAs. Upper: $\times 200$; middle and lower: $\times 400$; images of IgG and IgG4 are from almost the same fields.

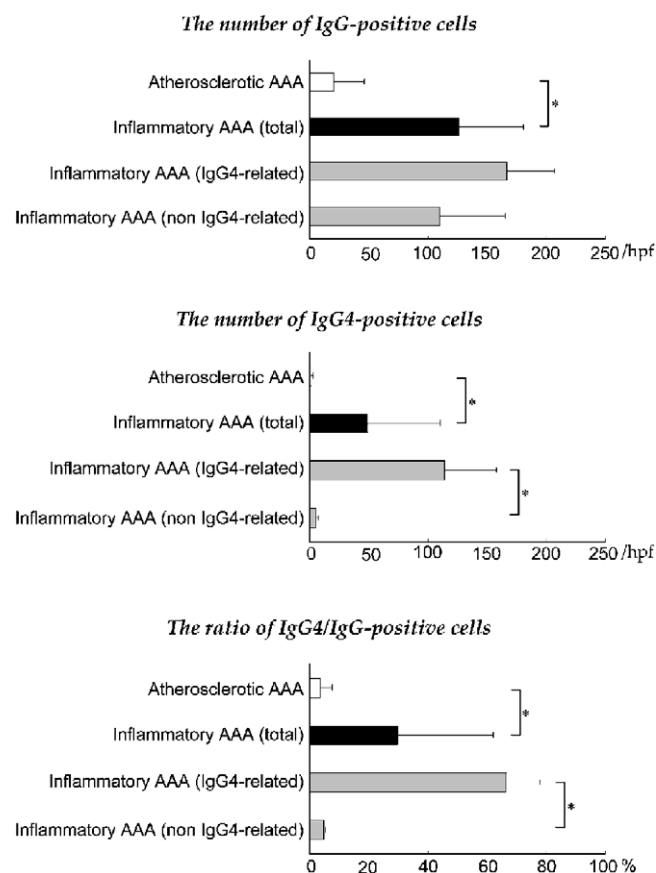


FIGURE 4. The numbers of IgG-positive or IgG4-positive plasma cells and the ratios of IgG4/IgG-positive plasma cells in inflammatory and atherosclerotic AAAs. The IgG-positive or IgG4-positive plasma cells are significantly more numerous in inflammatory AAA than atherosclerotic AAA. Comparing IgG4-related and nonrelated inflammatory AAAs, the numbers of IgG-positive plasma cells do not differ, although the numbers of IgG4-positive plasma cells and the ratios of IgG4/IgG-positive plasma cells are significantly higher in IgG4-related inflammatory AAA. *, $P < 0.05$.

among IgG4-related and nonrelated inflammatory AAAs, and atherosclerotic AAA (Table 2).

DISCUSSION

This study revealed that 4 of 10 patients with inflammatory AAA had numerous infiltrating IgG4-positive plasma cells and high serum IgG4 concentrations. All of those cases shared histologic characteristics of IgG4-related diseases, such as diffuse lymphoplasmacytic infiltration by many IgG4-positive plasma cells, irregular fibrosis, occasional eosinophilic infiltration, and obliterative phlebitis.^{10,13,29–31} Until recently, IgG4-related diseases occurring in various organs were called by different names such as autoimmune pancreatitis, sclerosing cholangitis, chronic sclerosing sialadenitis,

TABLE 2. Serum Concentrations of IgG, IgM, IgA, and IgG4, and ANA in Patients With Inflammatory and Atherosclerotic AAAs

	Normal Range	Inflammatory AAA		Atherosclerotic AAA (n = 22)
		IgG4-related (n = 3)	Non-IgG4-related (n = 3)	
IgG	870-1700	1570 ± 335	1423 ± 137	1446 ± 404
IgA	110-410	220 ± 53	353 ± 169	336 ± 226
IgM	35-220	114 ± 108	105 ± 79	93 ± 78
IgG4	4-110	260 ± 259†	42 ± 15	40 ± 21
ANA*	< 40 titer	33% (80)	67% (40)	45% (40-640)

*Data are shown as positive case ratios (range of titers).

† $P < 0.05$ vs. non-IgG4-related inflammatory AAA plus atherosclerotic AAA.

pulmonary or mammary inflammatory pseudotumor, prostatitis, and mediastinal or retroperitoneal fibrosis.^{13,28–31} However, they are now estimated to belong to a single disease entity named IgG4-related disease.¹⁰ The results of this study suggested that a subgroup of inflammatory AAA had clinicopathologic characteristics of IgG4-related disease, suggesting that they might be one of the IgG4-related diseases.

Since the initial description of inflammatory AAA in 1972, it has become clear that inflammatory AAA is one member of a family of disorders often referred to as “chronic periaortitis.”^{9,18,25} This family includes 3 members: inflammatory AAA, idiopathic retroperitoneal fibrosis, and a combination of the 2 disorders. In 2002, Hamano et al³ reported 3 patients having both autoimmune pancreatitis and retroperitoneal fibrosis. IgG4-positive cells could also be identified in the retroperitoneum of those patients, suggesting that IgG4-related immune reactions occurred in not only the pancreas but also the retroperitoneum.³ It is now widely accepted that IgG4-related retroperitoneal fibrosis can also occur in patients without other IgG4-related diseases.^{3,31} Taken together, IgG4-related inflammatory AAA could be estimated as “IgG4-related periaortitis” together with retroperitoneal fibrosis.

Interestingly, 6 patients with inflammatory AAA did not have abundant IgG4-positive plasma cells. That is, not all inflammatory AAAs seem to be IgG4-related. Leu¹⁴ and Rose and Dent²¹ described that inflammatory AAA was not clinicopathologically different from atherosclerotic AAA except for chronic inflammation and fibrosis. They concluded that inflammatory AAA is not separated from, but rather related to, atherosclerotic AAA. The non-IgG4-related inflammatory AAA in this study might correspond to those cases, because in 6 cases, non-IgG4-related inflammatory AAA pathologically resembled atherosclerotic AAA except for chronic inflammation and adventitial fibrosis. Non-IgG4-related inflammatory AAA and atherosclerotic AAA showed evident neutrophilic and inconspicuous eosinophilic infiltration, whereas IgG4-related inflammatory AAA was commonly associated with eosinophilic, but not

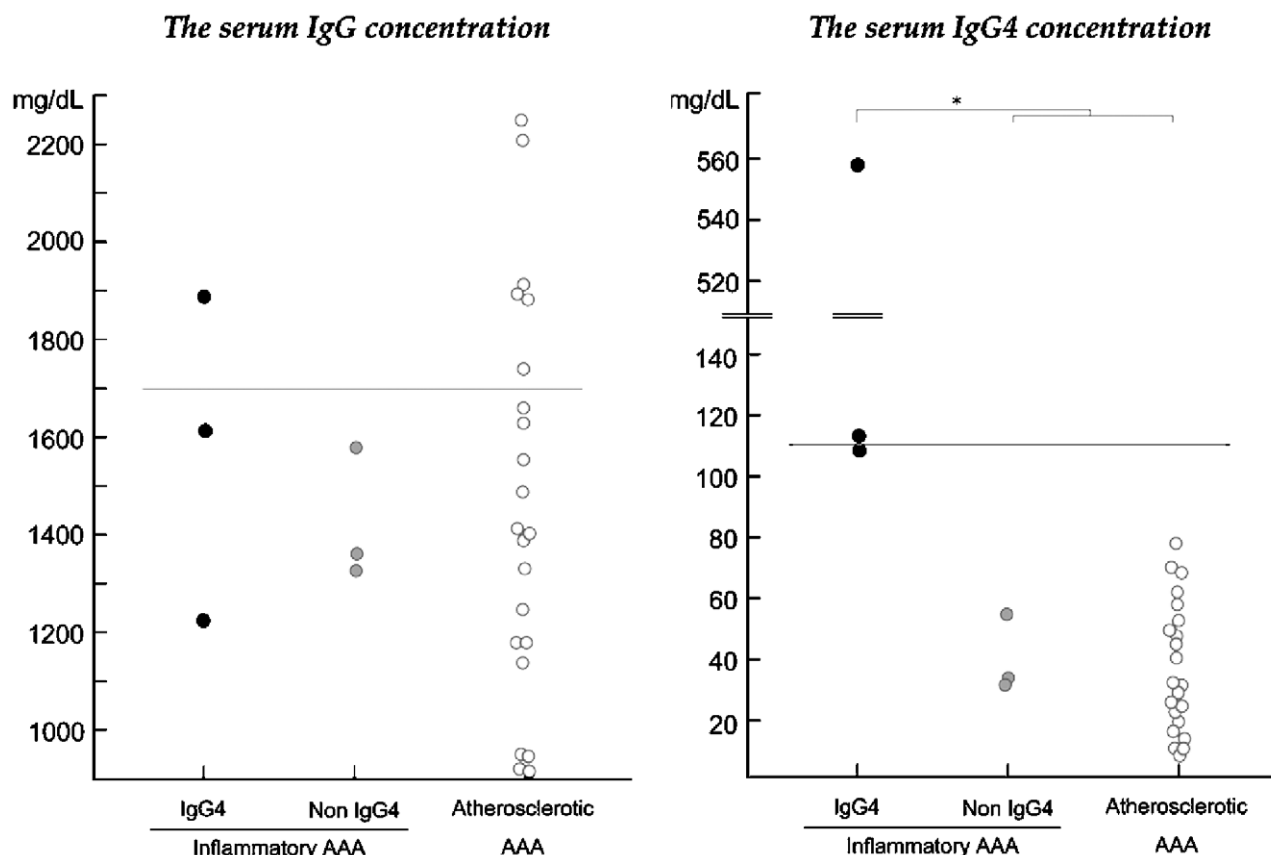


FIGURE 5. Serum concentrations of IgG and IgG4 in inflammatory (IgG4-related and nonrelated) and atherosclerotic AAAs. Serum IgG concentrations do not differ among the 3 groups. Serum IgG4 concentrations are elevated in 2 patients, both of which have IgG4-related inflammatory AAA. Serum IgG4 concentrations are significantly higher in patients with IgG4-related inflammatory AAA than those with non-IgG4-related inflammatory or atherosclerotic AAA. Horizontal bars, upper limits of the normal range. *, $p < 0.05$.

neutrophilic, infiltration. That is, non-IgG4-related inflammatory AAA might correspond to the inflammatory variant of atherosclerotic AAA.

Inflammatory AAAs could be pathologically classified into IgG4-related and nonrelated cases. A similar phenomenon was observed in sclerosing cholangitis. Sclerosing cholangitis without evident preceding conditions has been called primary sclerosing cholangitis.¹⁵ However, the same as this study, a pathologic study with regard to IgG4 revealed that a subgroup of patients with primary sclerosing cholangitis had numerous infiltrating IgG4-positive plasma cells.²⁹ Those patients are now estimated to have IgG4-related sclerosing cholangitis different from classic primary sclerosing cholangitis.¹⁶ The distinction between IgG4-related and nonrelated sclerosing cholangitis is clinically important, because IgG4-related diseases could well respond to steroid therapy the same as other IgG4-related diseases.^{4,7} In contrast, classic primary sclerosing cholangitis is a refractory disease. The effectiveness of steroid therapy has also been reported for inflammatory AAA.⁶ Sensitivity to steroids might differ between IgG4-related and nonrelated

inflammatory AAAs. Further clinic analysis seems mandatory to elucidate this important issue.

Recently, we performed a study on cytokine production in situ in patients with IgG4-related diseases.³² It was revealed that the expression of T_H2 (IL-4, IL-5, and IL-13) and regulatory cytokines (transforming growth factor- β and IL-10) was increased.³² We speculated that IL-10 is involved in increasing serum IgG4 concentrations and IgG4-positive plasma cell infiltration, because IL-10 has a major role in directing B cells to produce IgG4.^{8,17} transforming growth factor- β , which is a powerful fibrogenic cytokine, might participate in fibroplasia. Immune reactions in inflammatory AAA are still an enigma, although T_H2 or regulatory immune reactions might be increased in the aneurysm wall or periaortic soft tissue.

In conclusion, this study revealed that a subgroup of patients with inflammatory AAA had clinicopathologic characteristics such as numerous infiltrating IgG4-positive plasma cells and high serum IgG4 concentrations. This form of inflammatory AAA might belong to a disease entity of IgG4-related periaortitis.

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