A new clinicopathological entity of IgG4-related inflammatory abdominal aortic aneurysm

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Objective: **Recently, the relationship between immunoglobulin (Ig)G4 and idiopathic sclerosing lesions has attracted much attention. IgG4-related disease was first described with regard to the pancreas (autoimmune pancreatitis), and has been expanded to various organ systems. We previously reported that inflammatory abdominal aortic aneurysm (IAAA) could be one of the manifestations of IgG4-related disease. In this study, we tried to elucidate the clinical characteristics of IgG4-related IAAA.**
Methods: **This study consisted of 23 cases of IAAA and 40 cases of atherosclerotic abdominal aortic aneurysm (AAA). Clinical presentation, laboratory findings, and pathological features were examined. Aneurysms of 13 cases histologically corresponded to IgG4-related IAAA.**
Results: **Those cases accounted for 5% of all surgical AAAs, and 57% of IAAAs. Compared to non-IgG4-related IAAA, IgG4-related cases were characterized by less frequent association with abdominal or back pain. Serum IgG4 concentrations were significantly elevated in IgG4-related cases. Interestingly, patients with IgG4-related IAAA frequently showed an allergic constitution, such as drug allergy, autoimmune diseases, high serum IgE concentrations, and a high titer of antinuclear antibody. Pathologically, IgG4-related cases were characterized by more significant thickening of the adventitia and more numerous IgG4-positive plasma cell infiltrations. Three non-IgG4-related cases showed aneurysmal rupture at the time of first presentation, whereas no IgG4-related cases showed rupture.**
Conclusion: **Recognizing a new disease entity of IgG4-related IAAA seems important because this was clinically and pathologically different from conventional aAAA and non-IgG4-related IAAA. (J Vasc Surg 2009;49:1264-71.)**

Clinical Relevance: **IgG4-related disease was determined by irregular fibrous tissue proliferation with numerous infiltrations of IgG4-positive plasma cells and concentration of serum IgG4, and clinically characterized steroid sensitivity. We examined 23 cases of IAAA and 40 cases of aAAA, and revealed about half cases of IAAA was linked to the peri-aortic counterpart of IgG4-related disease. IgG4-related IAAA was clinicopathologically different from conventional aAAA and non IgG4-related IAAA, that is, IgG4-related IAAA was particularly characterized by frequency of complication of autoimmune diseases, low incidence of rupture, and high serum IgE concentration.**

Some abdominal aortic aneurysms (AAA) are characterized by diffuse thickness of the aneurysmal wall and extensive fibrous adhesion to adjoining tissues. In 1972, Walker et al first used the term inflammatory AAA (IAAA) to describe such aneurysms.[1] It was reported that IAAA is 2-10% of all AAA.[1,2] In comparison to atherosclerotic AAA (aAAA), IAAA has different clinical characteristics, such as younger age of the patients, symptoms such as backache, low-grade fever, or weight loss, and a larger diameter.[1-4]

Controversies exist regarding the cause and pathogenesis of IAAA. Some reports described that atherosclerotic aneurysm formation is the preceding phenomena, and that the inflammatory response is a secondary change;[5] that is, IAAA is the extreme end of an inflammatory process.[6,7] Other reports suggested the possible involvement of autoimmune reaction in the pathogenesis of IAAA.[8-10] Patients with IAAA sometimes show serological autoimmune abnormalities such as positive for auto-antibodies, or are associated with systemic autoimmune diseases.[10] In addition, several studies have suggested that IAAA may be due to an exaggerated immune response to infectious agents.[11,12] IAAA is now considered to be a heterogeneous disease entity.

Recently, a close relationship between immunoglobulin G4 (IgG4) and idiopathic sclerosing lesions has been suggested. IgG4-related sclerosing lesion, which is also

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called IgG4-related sclerosing disease (IgG4-SD), was first reported with regard to autoimmune pancreatitis (sclerosing pancreatitis).[13] This disease entity has been expanded to various organs, such as the bile duct,[14] salivary gland,[15] retroperitoneum,[16,17] and lung.[18] Irrespective of the organ of origin, IgG4-SD show common clinicopathologic features. Clinical characteristics of IgG4-SD are its frequent occurrence in adult male patients, elevation of serum IgG4 levels, and steroid sensitivity.[19,20] IgG4-SD is pathologically characterized by diffuse lymphoplasmacytic infiltration, irregular fibrosis, and obliterative phlebitis. Immunostaining of IgG4 reveals diffuse infiltration of IgG4-positive plasma cells.[14-18] In addition, some patients have multiple lesions in different organs at the same time or during follow-up;[19-21] that is, IgG4-SD is a systemic disorder, and each lesion is estimated as one of the manifestations of this systemic disorder.[21]

Recently, we pathologically examined IAAA from the viewpoint of IgG4.[22] We reported that some IAAA are IgG4-SD;[22] that is, IAAA could be classified into IgG4-related and non-related cases. IgG4-related cases showed elevated levels of serum IgG4 and diffuse infiltration of IgG4-positive plasma cells in the aneurysmal adventitia.[22] In contrast, non-IgG4-related cases had a more intense atherosclerotic reaction than IgG4-related cases; however, it has not been revealed whether any clinical differences exist between IgG4-related (IgG4-IAAA) and non-related IAAA (non-IgG4-IAAA). In particular, it seems important to know the steroid sensitivity or incidences of the rupture of IgG4-related and non-related cases, because they influence our therapeutic strategies for patients with IAAA.

In this study, we examined clinical and serological differences among aAAA, IgG4-IAAA, and non-IgG4-IAAA. The goal of this study is to reveal the clinical characteristics of IgG4-IAAA.

MATERIALS AND METHODS

The present study is approved by the human investigation review Committee of the University of Kanazawa (NO.468) and Kanazawa Medical Center (NO.248) and conforms to the principles outlined in the Declaration of Helsinki.

Case selection. During 1996 to 2007, we surgically treated 252 cases of AAA in our hospitals. In this study, we examined all cases of IAAA (23 cases) based on the pathological definition described below. From 2004 to 2007, 40 cases of aAAA were randomly selected as a disease control. Patients with suppurative infection (fungus and bacteria), vasculitis, or malignant tumors were excluded from this study.

Diagnosis of IAAA. Aneurysmal walls of all cases were histologically examined, and we diagnosed IAAA based on pathological findings (Fig 1). The explanted aneurysm wall in cases of IAAA showed diffuse fibrous thickening of the adventitia (more than 4 mm) with abundant lymphoplasmacytic infiltration. Pathologically diagnosed IAAA included all cases of clinically suspected IAAA (by pre- and/or intraoperative findings). Atheromatous degeneration and calcification were also observed in the intima, although fibrous and inflammatory changes in the adventitia were more conspicuous. The diagnosis of IgG4-IAAA was based on histologic findings of numerous IgG4 positive plasma cells (60/high-power field [hpf] and more than 60% of the IgG4/IgG-positive cell ratio) in the adventitia (Fig 2). The entire analysis of histological findings was performed by two pathologists (S.K. and Y.Z.) who were blinded to the clinical features of the sample.

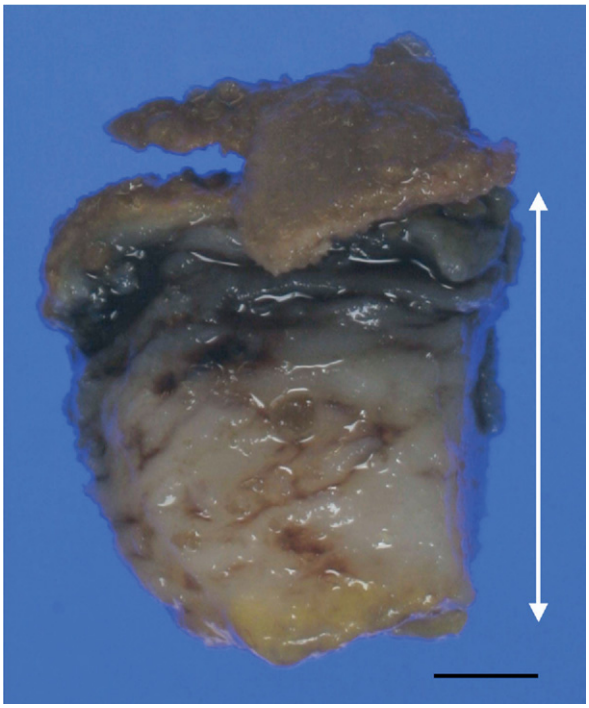

Fig 1. Macroscopic appearance of the abdominal aortic wall of IgG4-related inflammatory abdominal aortic aneurysm (IAAA) shows thickened fibrotic adventitia and periaortic tissues (*white arrow*). Scale bar:5 mm.

Risk factors and associated conditions. We examined the association with risk factors for AAA, such as a smoking habit, hypertension, diabetes, and hyperlipidemia using the preoperative clinical records of each patient retrospectively. A history of ischemic heart disease and autoimmune disorders was also examined. In addition, we examined whether patients had a history of allergic disorders, such as bronchial asthma and drug allergy, because recently the association between IgG4-SD and allergic reaction has been suggested.[23]

Laboratory examination. Within 1 month before surgery, all patients underwent routine laboratory evaluation, including white blood cell count (WBC), C-reactive protein (CRP), serum total protein, serum albumin, total choresterol, high-density lipoprotein (HDL) choresterol, low-density lipoprotein (LDL) cholesterol, and triglyceride. Preoperative serum samples were available for 6 cases of IgG4-IAAA, 4 cases of non-IgG4-IAAA, and all cases of

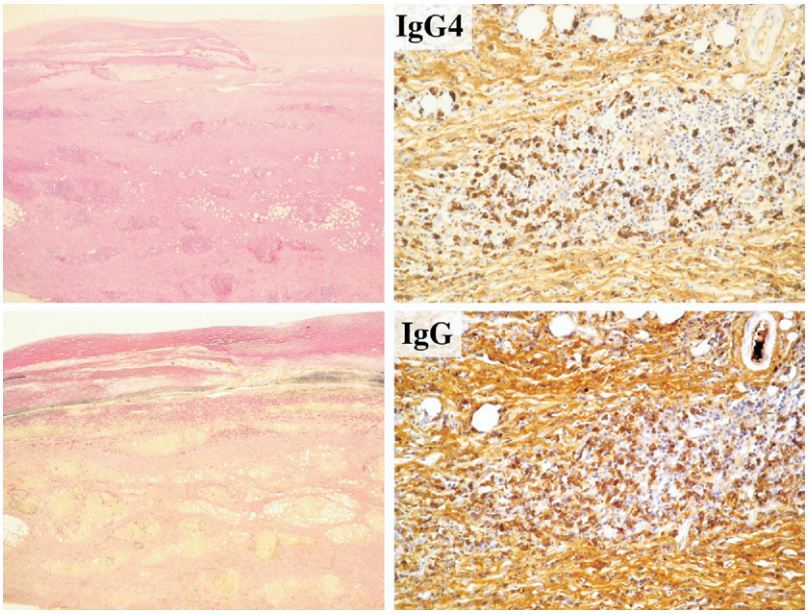

Fig 2. Histopathologic features of IgG4-related inflammatory abdominal aortic aneurysm (IAAA). Aneurysmal wall shows fibrous adventitial thickening with inflammatory cell infiltration (left upper, hematoxylin and eosin [H&E]; left lower, elastica van Gieson [EvG]; both images, ×20, in almost the same field). Immunostainings reveal numerous IgG+ and IgG4+ plasma cells in the adventitia (right images, ×200, in almost the same fields).

aAAA, and were used to examine IgG, IgG4, IgA, IgM, IgE, and antinuclear antibodies (ANA), and C3 and C4 complement fractures. All cases were selorogically negative for syphilis.

Histologic examination. Surgically resected specimens were fixed in neutral formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin (H&E) and elastica-van Gieson (EvG), and the rest were used for immunohistochemistry. Immunostaining of IgG and IgG4 was performed by an autostainer (HX System Benchmark, Ventana Medical Systems, Tucson, Ariz) 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, Calif). Sections were pretreated with proteinase. Negative controls were evaluated by substituting the primary antibody with similarly diluted nonimmunized mouse serum. IgG- and IgG4-positive plasma cells were counted in 5 different hpf (10 × eyepiece and 40 × lens) in 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 for each case. The intimal thickness (from the surface of atherosclerotic palque to inner elastic fiber of the media) and adventitial thickness (from outer elastic fiber of the media to the lowest part of the adventitia) were calculated on EvG-stained sections using a microscopic measure. In addition, we also examined whether the following seven histological features were evident: neutrophil infiltration (more than 10 per hpf), eosinophilic infiltration (more than 5 per hpf), plasma cell infiltration (more than 10 per hpf), lymph follicle with germinal center, obliterative phlebitis, granuloma formation, and perinueral inflammatory cell infiltration.

Intraoperative findings and postoperative outcome. We examined intraoperative findings based on the basis of a retrospective review of the operative notes of each surgeon. Complications within 30 days of surgery and long-term follow-up data were taken from the clinical records of each patient.

Statistics. Statistical analyses were performed using Fisher's test, the χ^2 test, when appropriate with the Yates correction, and the Mann-Whitney rank sum test for unpaired nonparametric data. Values of $P < .05$ were regarded as significant.

RESULTS

Clinical presentation. For 12 years (1996 to 2007), 252 cases of AAA were surgically treated in our hospitals. Histologic examination revealed that 23 cases (9% of 252 cases) corresponded to IAAA, and the remaining 229 cases were aAAA. Among 23 cases of IAAA, 13 cases histologically showed numerous IgG4-positive plasma cell infiltrations in the aneurysmal adventitia. Those cases were examined as IgG4-IAAA in this study. In contrast, the remaining 10 cases of IAAA had a few IgG4-positive plasma cells, and corresponded to non-IgG4-IAAA. Incidences of IgG4-IAAA and non-IgG4-IAAA were 5% and 4% of surgically treated AAA cases, respectively. IgG4-IAAA was 57% of IAAA.

Table I. Clinical characteristics of patients with atherosclerotic or inflammatory abdominal aneurysm

	AAA			*Inflammatory AAA*		
	Atherosclerotic (n = 40)	*Inflammatory (n = 23)*	P *value*	*IgG4-related (n = 13)*	*Non-IgG4-related (n = 10)*	P *value*
Age (years)	75 (56-87)	69 (59-81)	**.005**	70 (59-76)	69 (59-81)	.863
Gender (male/female)	32/8	20/3	.484	11/2	9/1	.704
Aneurysmal diameter (mm)	56 (27-100)	55 (28-100)	.100	58 (33-87)	52 (28-100)	.550
Symptoms						
Low grade fever	3 (8%)	9 (39%)	**.002**	5 (38%)	4 (40%)	.942
Abdominal or back pain	5 (13%)	6 (26%)	.175	1 (8%)	5 (50%)	**.025**
Rupture	3 (8%)	3 (13%)	.474	0	3 (30%)	**.038**
Death immediately after surgery	0	2 (1%)	.058	2 (15%)	0	.194

AAA, Abdominal aortic aneurysm.

Table II. Risk factors and associated conditions of abdominal aortic aneurysm

	AAA			*Inflammatory AAA*		
	Atherosclerotic (n = 40)	*Inflammatory (n = 23)*	P *value*	*IgG4-related (n = 13)*	*Non-IgG4-related (n = 10)*	P *value*
Smoking habit	28 (70%)	14 (61%)	0.463	7 (54%)	7 (70%)	.442
Hypertension	15 (38%)	6 (26%)	0.359	2 (15%)	4 (40%)	.192
Ischemic heart diseases	14 (35%)	8 (35%)	0.986	3 (23%)	5 (50%)	.189
Diabetes	10 (25%)	2 (9%)	0.075	1 (8%)	1 (10%)	.849
Hyperlipidemia	7 (18%)	4 (17%)	0.991	3 (23%)	1 (10%)	.412
Autoimmune diseases	5 (13%)	8 (35%)	**0.027**	7 (54%)	1 (10%)	**.025**
Drug allergy	5 (13%)	6 (26%)	0.171	5 (38%)	1 (10%)	.123
Bronchial asthma	3 (8%)	5 (21%)	0.102	4 (31%)	1 (10%)	.232

AAA, Abdominal aortic aneurysm.

Clinical characteristics of AAA cases are shown in Table 1. Patients with IAAA were significantly younger than those with aAAA. All patients underwent radiological examination by computed tomography (CT). Preoperatively, a CT scan revealed wall thickening or periaortic mass formation for the radiologic diagnosis of IAAA, in three cases of IgG4-IAAA (23%) and four cases of non-IgG4-IAAA (40%). Aneurysmal diameters were not different betweeen IAAA and aAAA. Small aneurysms (about 30 mm in diameter) were resected due to their saccular form, and were detected in one case of IgG4-IAAA and one case of non-IgG4-IAAA. Several cases of IgG4-IAAA showed a trend toward irregular thickening of the abdominal wall by retrospective radiological re-examination. Iliac arteries were involved in 6 patients with aAAA (15%), 1 patient with IgG4-IAAA (8%), and 1 patient with non-IgG4-IAAA (10%).

Twelve patients with IAAA (52%) presented with constitutional symptoms such as low-grade fever (37-37.5°C) dull abdominal or back pain, fatigue, anorexia, and weight loss over several months, whereas the remaining cases were incidentally found to have AAA during routine medical examinations or work-ups for other diseases. Abdominal or back pain was more commonly observed in patients with non-IgG4-IAAA cases compared to IgG4-IAAA cases (50% vs 8%, $P = .025$). Aneurysmal rupture was observed in 3 patients with IAAA. Interestingly, all were non-IgG4-IAAA cases. Aneurysmal rupture was more common in non-IgG4-IAAA than IgG4-IAAA (30% vs 0%, $P = .038$).

Risk factors and associated conditions. Incidences of risk factors and associated conditions of AAA are shown in Table II. Incidences of a smoking habit, hypertension, ischemic heart diseases, hyperlipidemia, and allergic disorders were not different between patients with aAAA and IAAA. All patients with a medical history of hyperlipidemia were treated with statins. Comparing IgG4-IAAA and non-IgG4-IAAA, a smoking habit, hypertension, ischemic heart diseases, and diabetes were slightly less common in IgG4-IAAA. In contrast, allergic and autoimmune diseases were frequently observed in IgG4-IAAA. Five patients with IgG4-IAAA had drug allergies (2 patients, cefazolin sodium; 2 patients, xylocaine; 1 patient, contrast medium iopronide). Four patients had a history of bronchial asthma. In addition, 7 patients with IgG4-IAAA had autoimmune diseases (3 patients, rhumatoid arthritis; 2 patients, idiopathic thrombocytopenic purpura; 1 patient, Sjögren's disease; antiphospholipid antibody syndrome) with a significantly higher incidence. In patients with non-IgG4-IAAA, 1 patient was complicated with chronic renal failure and 1 patient with alcoholic liver injury, while these injuries were not detected in patients with IgG4-IAAA, no patients examined in this study had any history of IgG4-SD at other sites. No patients were treated with corticosteroids before surgery.

Table III. Laboratory findings of patients with abdominal aortic aneurysm

		AAA			*Inflammatory AAA*		
		Atherosclerotic	*Inflammatory*	P-*value*	*IgG4-related*	*Non-IgG4-related*	P-*value*
White blood cell count (WBC)	(/μL)	5938 ± 1854	8369 ± 3818	**< .001**	8739 ± 2689	7890 ± 5054	.609
C-reactive protein (CRP)	(mg/dL)	0.4 ± 0.9	3.1 ± 2.2	**< .001**	2.6 ± 2.2	3.8 ± 2.2	.485
Total protein	(g/dL)	6.9 ± 0.6	6.5 ± 0.8	**.023**	6.6 ± 0.7	6.4 ± 0.9	.469
Albumin	(g/dL)	4.2 ± 0.6	3.3 ± 0.9	**< .001**	3.4 ± 0.9	3.3 ± 0.9	.789
IgG*	(mg/dL)	1403.8 ± 407.1	1462.6 ± 369.9	.680	1474.8 ± 295.1	1444.3 ± 514.6	.907
IgG4*	(mg/dL)	36.9 ± 23.9	173.2 ± 92.9	**< .001**	273.5 ± 91.6	22.8 ± 13.4	**.034**
IgA*	(mg/dL)	338.8 ± 254.8	335.5 ± 128.8	.969	333.3 ± 134.1	339.3 ± 140.7	.945
IgM*	(mg/dL)	94.3 ± 64.5	94.0 ± 79.6	.991	110.0 ± 34.7	70.0 ± 55.4	.469
IgE*	(IU/mL)	212.5 ± 51.7	685.4 ± 867.4	**.029**	1124.3 ± 881.9	27.1 ± 12.9	**.041**
Antinuclear antibody*	(>40 titers)	2 (4% of cases)	4 (40% of cases)	**.039**	3 (50% of cases)	1 (25% of cases)	.303
Antinuclear antibody*	(>320 titers)	1 (2% of cases)	2 (20% of cases)	**.019**	2 (33% of cases)	0	**.023**
C3*	(mg/dL)	141.8 ± 29.9	142.6 ± 43.4	.940	138.5 ± 45.0	148.8 ± 46.8	.738
C4*	(mg/dL)	32.5 ± 9.4	32.5 ± 7.2	.988	34.8 ± 8.3	28.9 ± 3.6	.225
Total cholesterol	(mg/dL)	180.9 ± 34.8	173.3 ± 45.2	.484	157.5 ± 42.9	194.4 ± 41.2	.618
HDL cholesterol	(mg/dL)	40.3 ± 9.5	48.3 ± 9.8	.800	48.3 ± 11.3	48.3 ± 7.2	.161
LDL cholesterol	(mg/dL)	100.9 ± 29.3	98.4 ± 22.1	.814	96.3 ± 23.5	102.7 ± 22.9	.713
Triglyceride	(mg/dL)	126.9 ± 63.1	96.9 ± 42.1	.073	83.1 ± 36.8	118.7 ± 43.1	.079
AST	(IU/L)	23.4 ± 13.0	40.4 ± 54.8	.064	46.3 ± 71.1	32.8 ± 22.2	.578
ALT	(IU/L)	18.4 ± 12.5	29.6 ± 29.9	.042	30.2 ± 36.1	28.7 ± 21.1	.91
γ-GTP	(IU/L)	36.7 ± 49.9	45.5 ± 45.2	.487	46.6 ± 52.4	48.00 ± 36.4	.834
ALP	(IU/L)	252 ± 108.7	287 ± 163	.306	301 ± 194	269 ± 119	.653
PT	INR	1.16 ± 0.17	1.22 ± 0.31	.383	1.19 ± 0.18	1.26 ± 0.43	.622
Blood urea nitrogen	(mg/dL)	20.3 ± 11.5	18.5 ± 7.5	.511	17.5 ± 5.7	19.7 ± 9.6	.503
Creatinine	(mg/dL)	1.2 ± 1.1	1.1 ± 0.6	.079	1.0 ± 0.4	1.3 ± 0.8	.276

AAA, Abdominal aortic aneurysm; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *AST,* aspartate aminotransferase; *ALT,* alanine aminotransferase; *γ-GTP,* γ-glutamyl transpeptidase; *ALP,* alkaline phosphatase; *PT,* prothrombin time.

*Preoperative serum samples were available in 6 cases of IgG4-related inflammatory AAA, 4 cases of non-IgG4 related inflammatory AAA, and all cases of atherosclerotic AAA.

Laboratory findings. The results of serological examination are shown in Table III. The WBC and CRP in patients with IAAA were significantly higher than those with aAAA. Serum total protein and albumin were lower in IAAA patients statistically. ANA was more frequently detected in IAAA cases. In particular, high titers of ANA (more than 320) were detected in two cases (40%) of IgG4-related IAAA, whereas the titer of ANA was low (0-80) in patients with aAAA or non-IgG4-IAAA, except one. Comparing patients with IgG4-IAAA and non-IgG4-IAAA cases, only serum IgG4 and IgE levels were significantly different. Serum IgG4 concentrations were significantly elevated in patients with IgG4-IAAA (average, 274; range, 109-559; normal range, ≤110 mg/dL) compared to non-IgG4-IAAA (average, 23; range, 8-36). Interestingly, serum IgE concentrations were also elevated in all patients with IgG4-IAAA (average, 1124 IU/mL; range, 242-2300; normal range, <200), but not in any cases of non-IgG4-IAAA (average, 27; range, 3-78). Serum concentrations of other immunoglobulins, C3 and C4 complements, lipid factors, and the functional markers of the liver and kidney were not different among the three groups.

Pathological findings. Pathological findings are summarized in Table IV. IAAA was pathologically characterized by marked fibrous thickening of the adventitia. Notably, IgG4-IAAA showed significantly thicker adventitia than non-IgG4-IAAA ($P = .033$). In the adventitia of inflammatory cases, diffuse lymphoplasmacytic infiltration was observed and it was associated with storiform fibrosis. Of 13 cases of IgG4-IAAA, 12 had obliterative phlebitis, which is one of the characteristic pathologic findings of IgG4-SD in the adventitia. In addition, as mentioned in our previous study,[22] IgG4-IAAA was characterized by the frequent infiltration of eosinophils, lymphoid follicle formation, perineural inflammatory extension, and inconspicuous infiltration of neutrophils compared to non-IgG4-IAAA. Atherosclerotic intimal thickening with or without calcification was a characteristic feature of aAAA, and it was more conspicuous in non-IgG4-IAAA than in IgG4-IAAA ($P = .012$). Immunostaining of IgG4 revealed diffuse infiltration of IgG4-positive plasma cells in the adventitia in IgG4-IAAA. The number of IgG4-positive plasma cells and the ratio of IgG4/IgG-positive plasma cells were significantly higher in IgG4-IAAA than in aAAA or non-IgG4-IAAA.

Intraoperative findings. All patients underwent graft replacement surgical procedures. The surgeons identified the characteristic white glistening perianeurysmal fibrosis in seven cases (30%) of IAAA but in no aAAA ($P < .001$). In our impression, no clear differences between IgG4-IAAA and non-IgG4-IAAA were apparent in macroscopic findings. At the time of surgery, perianeurysmal fibrosis was

Table IV. Pathological findings of atherosclerotic and inflammatory abdominal aortic aneurysm

		AAA			*Inflammatory AAA*		
		Atherosclerotic (n = 40)	*Inflammatory (n = 23)*	P *value*	*IgG4-related (n = 13)*	*Non-IgG4-related (n = 10)*	P *value*
Adventitial thickening	(mm)	0.46 ± 0.34	4.91 ± 1.66	**< .001**	5.58 ± 1.56	4.11 ± 1.45	**.033**
Intimal thickening	(mm)	2.3 ± 1.0	1.4 ± 0.9	**.003**	1.04 ± 0.61	1.99 ± 0.96	**.012**
IgG^+ cells	(/hpf)	62.7 ± 52.1	95.8 ± 37.4	**.011**	110.2 ± 35.4	78.6 ± 33.6	**.046**
$IgG4^+$ cells	(/hpf)	9.5 ± 6.2	55.2 ± 44.8	**< .001**	88.5 ± 32.13	15.3 ± 13.2	**< .001**
$IgG4^+/IgG^+$ cell ratio	(%)	10.4 ± 13.8	51.3 ± 38.8	**< .001**	80.2 ± 3.2	17.6 ± 4.5	**< .001**
Neutrophils	(>10/hpf)	23 (58%)	8 (35%)	.083	1 (8%)	7 (70%)	**.002**
Eosinophils	(>5/hpf)	0	12 (52%)	**< .001**	11 (85%)	1 (10%)	**.001**
Plasma cells	(>10/hpf)	14 (35%)	19 (83%)	**< .001**	13 (100%)	6 (60%)	**.012**
Lymphoid follicle		4 (10%)	19 (83%)	**< .001**	13 (100%)	3 (30%)	**< .001**
Obliterative phlebitis		1 (3%)	16 (70%)	**< .001**	12 (92%)	4 (40%)	**.002**
Perineural inflammation		2 (5%)	15 (65%)	**< .001**	12 (92%)	3 (30%)	**.002**

AAA, Abdominal aortic aneurysm; *hpf,* high-power field

similarly identified in both IgG4-IAAA (3 cases, 40%) and non-IgG4-IAAA (4 cases, 31%), while tighter adhesion to surrounding structures of the abdominal aorta (duodenum and retroperitoneum) was noted in two cases of IgG4-IAAA.

Postoperative outcome. Two patients (15%) with IgG4-IAAA died within 30 days after surgery. One patient died of duodenal rupture and acute peritonitis on the third postoperative day, probably due to tight fibrous adhesion of abdominal aorta and the duodenum. The other patient was complicated with bronchial pneumonia and infective seroma in the lateral abdomen after surgery. This patient died of candida infection on the twentieth postoperative day. In contrast, all patients with aAAA and non-IgG4-IAAA were alive 30 days after surgery. No differences with regard to perioperative complications or reoperation were found among the three groups.

DISCUSSION

In this study, we examined the clinical characteristics of IgG4-IAAA. The obtained results could be summarized as follows: (1) IgG4-IAAA is 5% of total surgical AAA cases, and 57% of IAAA. (2) Aneurysmal rupture in IgG4-IAAA was less frequent than that in non-IgG4-IAAA. (3) Patients with IgG4-IAAA were associated with allergic or autoimmune disorders. (4) Serum IgG4 and IgE concentrations and ANA (>320 titers) were useful for discriminating between IgG4-IAAA and non-IgG4-IAAA. (5) As described in our previous study,[22] IgG4-IAAA is pathologically characterized by adventitial thickening with numerous IgG4-positive plasma cell infiltration and obliterative phlebitis.

It is surprising that 5% of surgical AAA cases were IgG4-IAAA. Before starting this study, we speculated that IgG4-IAAA was not a common disorder; however, this study revealed that more than half of IAAA cases were IgG4-related. The precise incidence of IgG4-related cases in AAA, including non-surgical cases, is still unknown, but testing serum IgG4 concentrations could be a useful non-invasive method to diagnose IgG4-IAAA, as for other IgG4-SD.

IgG4-SD has similar clinical characteristics irrespective of the organ of origin.[13-22] The most important clinical characteristic is steroid sensitivity. IgG4-SD usually manifests as pseudo-tumorous swelling of the affected organ, and some have been called inflammatory pseudotumor.[14,18,24] IgG4-SD dramatically responds to steroid therapy for 2 or 3 weeks.[20] It is an important issue whether or not steroid therapy is useful for IgG4-IAAA, as for other organs. In this study, no patients were examined to treat by steroids, although it is speculated that adventitial thickening could be reduced by steroid therapy. Preoperative steroid therapy might be useful to reduce retroperitoneal fibrous adhesion, which could reduce the surgical risk; however, the risk of aneurysmal rupture might be elevated by thinning the adventitia. The balance between reducing retroperitoneal adhesion and the risk of rupture seems important. Further investigations are mandatory to conclude how we should use steroids during the medical management of IgG4-IAAA.

At surgery, owing to dense fibrous adherence to the surrounding structures of the abdominal aorta, IAAA makes dissection difficult, and inadvertent entry may lead to fatal complications.[4] The mortality rate in aAAA was reported 3-4%.[2] Among the three groups, only the subgroup of patients with IgG4-IAAA (2 cases) died within 30 days after surgery with a high mortality rate (15%), probably because tighter fibrous adhesion in IgG4-IAAA causes more surgical difficulties. We expected that an endovascular approach together with steroid therapy would be appropriate management for IgG4-IAAA.

Before now, the interpretation of IAAA was controversial. IAAA was estimated as an extreme end of aAAA by some investigators,[5-7] whereas others suggested an autoimmune or infectious pathogenetic process in IAAA.[8-12] We pathologically examined IAAA with regard to IgG4-SD, and concluded that IAAA could be classified into two types: IgG4-related and non-related cases.[22] We speculate that

IgG4-IAAA is a unique aneurysm associated with IgG4-related immune reaction, and could be one of the manifestations of IgG4-SD. It seems important to clearly discriminate between IgG4-related or non-related cases among IAAAs, because those two conditions have different clinicopathological characteristics. In particular, the risk of aneurysmal rupture or steroid sensitivity might be different between them.

Interestingly, patients with IgG4-IAAA were frequently complicated with allergic disorders, such as bronchial asthma or drug allergy. In addition, serum IgE concentration was significantly elevated in IgG4-related cases. The detailed immune reaction in IgG4-SD is still controversial, and the mechanisms of IgG4-positive plasma cell infiltration and elevation of serum IgG4 concentrations have not been elucidated so far; however, the relationship between IgG4-SD and allergy-like immune reactions has attracted much attention.[23] Recently, we performed a study on cytokine production in situ in IgG4-SD.[25] It was revealed that the expression of Th2 (IL-4, IL-5, IL-13) and regulatory cytokines (transforming growth factor [TGF]-β and IL-10) was increased in IgG4-SD.[25] Th2-dominate immune reactions observed in IgG4-SD were different from most autoimmune diseases, which are usually characterized by a Th1-dominate reaction,[26,27] and rather resembled allergic immune reaction.[28] In addition, we speculated that IL-10 might participate in increasing serum IgG4 concentrations and IgG4-positive plasma cell infiltration, because IL-10 has a potent function in directing B cells to produce IgG4.[29,30] TGF-β, which is a powerful fibrogenic cytokine, might participate in fibroplasia.[31] Immune reactions in IAAA are still an enigma, although Th2 or regulatory immune reactions might be increased in the aneurysm wall or periaortic soft tissue. These unique immune reactions might induce the elevation of serum IgG4 and IgE concentration in patients with IgG4-IAAA.

We revealed an association with autoimmunity in IgG4-IAAA, that is, a significantly higher incidence of autoimmune diseases and frequent presence of ANA, compared to two other groups of AAA. Especially in two patients with IgG4-IAAA, the titer of ANA was so high (more than 320). Although ANA positivity was detected in non-IgG4-IAAA, the titer of ANA was low (40-80) and would be nonspecific. Autoantibodies including ANA and rheumatoid factor were also frequently observed in IgG4-SD.[20,21] Therefore, the significance of the high titer of ANA is also a useful laboratory sign in screening for IgG4-IAAA.

We found non-IgG4-IAAA had some clinicopathological resemblance to aAAA. Indeed Rose and Dent[6] explained that IAAA was the extreme end of the inflammatory process of aAAA, because of no sharp distinction between aAAA and IAAA. However, considering the autoimmune aspects of non-IgG4-IAAA, we approved of other hypotheses such as autoimmune reactions against the local antigens, such as oxidized low-density lipoproteins and ceroid in atherosclerotic plaque.[10] Through highly destructed intima and media of the aortic wall, the long-term leakage of serum-unknown antigens would be involved in chronic inflammation. Another possible causal factor was chronic continuous infections in the aortic wall, for instance, C*hlamydia pneumonia* and *Cytomegalovirus.*[11,12] Under recognition of the different subgroups of IAAA, further studies are needed to reveal the pathogenesis of non-IgG4-IAAA.

In conclusion, the present study revealed that IgG4-IAAA is not so rare. It seems important to precisely diagnose IgG4-IAAA, because the clinicopathological characteristics of those patients were different from those with aAAA and non-IgG4-IAAA.

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AUTHOR CONTRIBUTIONS

Conception and design: SK, YZ
Analysis and interpretation: SK, YZ
Data collection: SK, ME, YM, FK
Writing the article: SK, YZ
Critical revision of the article: SK
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INVITED COMMENTARY

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Elevated serum immunoglobulin-G4 (IgG4) has been linked to several overlapping syndromes that are related to IgG4-producing plasma cells. These clinical syndromes include cholangitis, autoimmune hepatitis and pancreatitis, Sjögren's syndrome, nephritis, and retroperitoneal fibrosis, and the spectrum of this disease has been labeled "IgG4-related systemic disease." Management of IgG4-related systemic disease generally includes immunosuppressive therapy; dramatic responses to medical therapy have obviated surgical management in many cases.

Inflammatory aneurysms have long proved to be challenging for vascular surgeons, with chronic periaortitis, inflammation, and fibrosis increasing the difficulty of surgical repair, and, possibly paradoxically, reducing the risk of rupture. The authors have previously published their examination of a small series (n = 10) of inflammatory aneurysms, and showed that four of the 10 inflammatory aneurysms had abundant IgG4-positive plasma cells and histological changes typical of IgG4-related systemic disease. In this paper, the authors expand their examination to the 23 cases of inflammatory aneurysms that were treated over 12 years, 13 cases of which contained IgG4-positive plasma cells. These patients were associated with reduced risk of rupture, other allergic or autoimmune disorders, and positive serology for IgG4, IgE, and antinuclear antibody (ANA), compared with the 10 cases that did not contain IgG4-positive plasma cells.

The implications of this report suggest that IgG4-related inflammatory aneurysms may be treated medically, rather than surgically; conversely, the high rate of rupture in IgG4-negative aneurysms suggests an aggressive therapeutic approach is warranted. Optimal medical and surveillance strategies need to be defined for IgG4-related aneurysms, and optimal surgical strategies, that minimize complication risk, need to be defined for IgG4-negative aneurysms. As the only other report of IgG4-related inflammatory aneurysm disease has come from another Japanese group,[1] the utility of these observations will be clarified as they are extended to other populations.

There are implications for other vascular diseases as well. For example, Kawasaki disease is an acute inflammatory childhood vasculitis with intense secretion of cytokines that permanently damage the vascular endothelium and typically result in coronary aneurysms. This disease is usually treated with immune globulin and aspirin, with steroid therapy being controversial. Should Kawasaki disease prove to be IgG4-related, then additional insights into its management will be obtained.

Ultimately, the increasing importance of the role of the immune system in the pathogenesis of atherosclerosis is being recognized. If IgG4-related systemic disease plays a causative role in the formation of atherosclerosis in even a small subset of patients, medical therapy for this important vascular disease may ultimately prove to be a reality.

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