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Original Article

Prevalence of Elevated Serum IgG4 Level among Patients Diagnosed or Suspected with Cardiovascular Disorders

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Immunoglobulin G4 (IgG4)-related disease, that is characterized by the elevation of circulating IgG4 level and the tissue-infiltration of IgG4-positive plasma cells, can target the cardiovascular tissue, although the diagnosis of IgG4-related cardiovascular lesion is not easy owing to the substantial risk for the tissue sampling. We herein examined the serum IgG4 levels among cardiac patients. In patients who were admitted to the cardiology department (n=477) and those who underwent computed tomography coronary artery angiography (n=401), elevated serum IgG4 level (≥135 mg/dL) was found 23 (4.8%) and 17 (4.2%), respectively. However, among those with elevated serum IgG4, only two patients could be clinicopathologically diagnosed with IgG4-related disease. Cardiovascular organ involvement may aggravate the prognosis of IgG4-related disease which in general not life-threatening. Considering that the non-negligible prevalence of high IgG4 level among cardiac patients who were not diagnosed with IgG4-related disease, however, physicians should not count too much on the serum IgG4 levels for the diagnosis of IgG4-related cardiovascular lesions, especially when histopathologic findings are not available, or when other-tissue involvement of IgG4-related disease is not apparent. (This is a translation of J Jpn Coll Angiol 2017; 57: 91–98.)

Keywords: IgG4-related disease, serum IgG4, diagnosis, cardiovascular

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a new clinicopathological entity, which was first reported in 2001 in the case of autoimmune pancreatitis by Hamano et al. in Japan.[1)] IgG4-RD is characterized by elevated serum immunoglobulin G4 (IgG4) level, diffuse or localized tissue thickening that forms tumefactive lesions, tissue infiltration of lymphocytes and IgG4-positive plasma cells. IgG4-RD may appear in various organs throughout the body either synchronously or metachronously.[2)] In Japan, IgG4-RD was designated as an intractable disease in July 2017 (http://www.nanbyou.or.jp/entry/4505).

It was shown that some, albeit not all, instances of periaortitis, periarteritis, inflammatory aortic aneurysm, and mediastinal fibrosis may occur as part of the IgG4-RD spectrum.[3–5)] For example, Kasashima et al. showed in their histopathologic study that some cases of inflammatory aortic aneurysms can be categorized as IgG4-RD.[6)] In addition, Perugino et al. more recently reported several cases of IgG4-related vasculitis affecting the aorta and peripheral arteries including coronary, carotid, and iliac arteries, indicating that large vessel vasculitis is one of the features of IgG4-RD.[7)]

As the concept of IgG4-RD became widely acknowledged, measurement of serum IgG4 level is more frequently performed among patients who are suspected of having IgG4-RD. Hamano et al. reported that, when the serum IgG4 of 135 mg/dL or higher is set as the cut-off level, autoimmune pancreatitis (IgG4-RD) can be differentiated from other non-IgG4-related pancreatic diseases, such as pancreatic cancer, with a high sensitivity (95%) and a high specificity (97%).[1)] To date, it is not known whether this cut-off level (135 mg/dL) provides a strong enough ground for diagnosing IgG4-related vasculitis among various cardiovascular disorders. In the present study, we measured serum IgG4 levels in patients with various cardiovascular

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disorders, and determined the range of serum IgG4 levels among them.

Subjects and Methods

Subjects: This study was approved by the Institutional Review Board of Osaka Medical College. After obtaining written informed consent, serum IgG4 levels were measured in patients who were admitted to the Department of Cardiology and in those who underwent electrocardiography (ECG)-gated computed tomography (CT). Medical records in these patients were checked whether patients had been diagnosed or suspected with IgG4-RD in cardiovascular or in other organs.

Measurement of IgG4 levels: Measurement of IgG4 levels was outsourced to LSI Medience Co. (Tokyo, Japan).

Statistical analyses: Statistical analyses were conducted using SPSS Statistics version 22 (IBM, New York, NY, USA).

Results

This study included 477 patients who were admitted to the cardiology department (inpatient group) and 401 patients who underwent ECG-gated CT (CT group). ECG-gated CT was performed mainly for the evaluation of coronary artery. Forty-four patients were found to be included in both groups; however, due to the difference in the timing of blood sampling, serum IgG4 value was not identical for the same patient.

Cardiology inpatients

Patient clinical features and serum IgG4 levels

Table 1 demonstrates clinical features of inpatient group. The correlation of serum IgG4 with albumin/globulin (A/G) ratio among 477 inpatients is shown in **Fig. 1**, and serum IgG4 levels of these patients are shown in **Fig. 2A**. In men, the median IgG4 level was 40.4 mg/dL (interquartile range [IQR], 19.4–65.6 mg/dL), which was significantly higher than that in women (median, 26.2 mg/dL; IQR, 16.3–47.6 mg/dL, P = 0.001, Mann–Whitney test). Overall, 23/477 (4.8%) patients were found to have IgG4 levels ≥ 135 mg/dL, and elevated IgG4 level was significantly more prevalent in men (22/341 [6.5%]) than in women (1/136 [0.7%], P = 0.007, Chi-square test). Case no. 14 of inpatient group (InPt-case 14) had been diagnosed with Mikulicz disease before enrollment of the study, and case no. 3 (InPt-case 3) had been diagnosed with IgG4-related coronary periarteritis at our department (**Table 2**). No other patients had previously been diagnosed with IgG4-RD at the time of study enrollment.

Serum IgG4 levels were significantly correlated with serum total protein (TP) (r = 0.16, P < 0.001), albumin (Alb) (r = −0.10, P = 0.026), and A/G ratio (r = −0.11,

Table 1 Characteristic of cardiac inpatients

No. of subjects	477
Age, years	68.4±10.8
Women, n (%)	136 (28.5)
BMI, kg/m^2	23.3±3.4
Systolic blood pressure, mmHg	127±19
Chronic hemodialysis, n (%)	11 (2.3)
Smoking status	
Never (%)	113 (83.1)
Former (%)	19 (14.0)
Current (%)	4 (2.9)
Cardiovascular disease	
Ischemic heart disease, n (%)	304 (63.7)
Arrhythmic disease, n (%)	105 (22.0)
Peripheral artery disease, n (%)	41 (8.6)
Valvular heart disease, n (%)	61 (12.8)
Cardiomyopathy, n (%)	32 (6.7)
Aneurysmal disease, n (%)	31 (6.5)
Laboratory data	
White blood cell count, ×10^3/μL	6.2±1.9
Hemoglobin, g/dL	13.2±1.7
Platelet count, ×10^4/μL	22.0±6.4
Total protein, g/dL	6.9±0.6
Albumin, g/dL	3.9±0.4
IgG4, median (IQR) mg/dL	34.2 (18.4–59.5)
Creatinine*, mg/dL	0.96±0.52
eGFR*, mL/min/1.73 m^2	51.8±20.4
C-reactive protein, median (IQR) mg/dL	0.11 (0.04–0.40)

*Excluding those with hemodialysis.
Data are presented as the mean±standard deviation or the median and interquartile range (IQR).

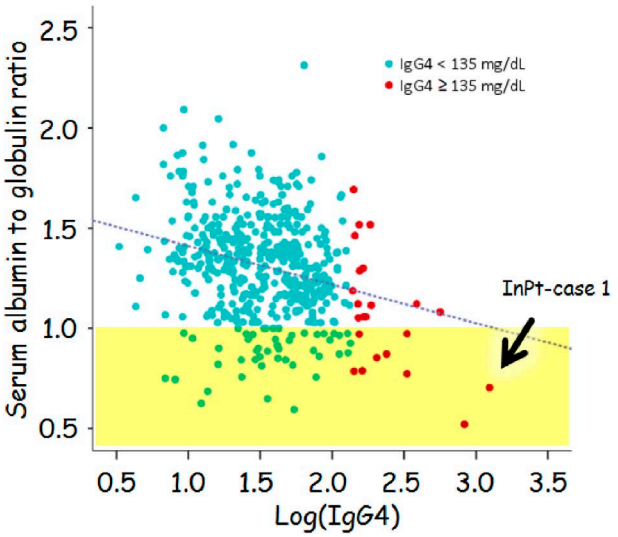

Fig. 1 Correlation between serum IgG4 and albumin/globulin ratio among cardiology inpatients.
Serum IgG4 showed negative correlation with albumin/globulin ratio. InPt-case 1 had the highest serum IgG4 value among the studied cardiology inpatients.

P=0.017, Spearman's test) (**Fig. 1**). Among 52 patients with low A/G ratio (<1.0), high serum IgG4 levels (≥135 mg/dL) was observed in 9 (17%) patients, the prevalence of which was significantly greater than that among 425 patients with an A/G ratio of ≥1.0 (14 patients [3.3%], P<0.0001, Chi-square test). Relationship between serum IgG4 and A/G ratio remained statistically significant even after excluding those who had low serum albumin (<3.9 mg/dL) from the analysis (r=−0.21, P<0.001, Spearman's test). Serum IgG4 levels were not significantly correlated with age (r=0.04, P=0.429), body mass index, white blood cell count, hemoglobin, platelet (PLT) count, or uric acid. In InPt-case 3, who had been diagnosed with IgG4-related coronary periarteritis, serum TP and Alb levels were 4.0 g/dL and 7.7 g/dL, respectively, and A/G ratio was 1.08.

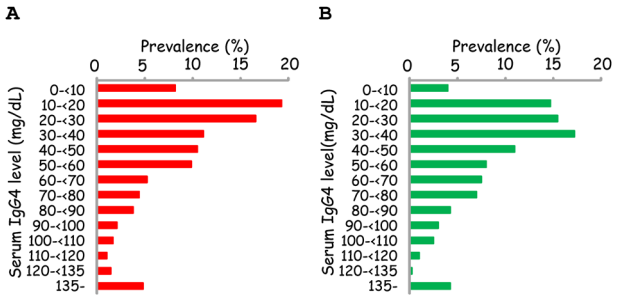

Fig. 2 Distribution of the serum IgG4 levels.
A. IgG4 levels among cardiac inpatients. **B**. IgG4 levels among patients who underwent ECG-gated computed tomography (CT). Increased IgG4 (≥135 mg/dL) was observed in 4.8% or the cardiac inpatients and 4.2% of those undergoing ECG-gated CT.

The cardiovascular diseases that led to hospitalization of the 23 patients with elevated serum IgG4 levels and accompanying conditions are described in **Table 2**. We reported, in the previous paper, two cases in the list; InPt-case 3 who had been diagnosed with IgG4-related coronary periarteritis,[8,9] and InPt-case 7 (the same as CT-case 5) who were initially diagnosed with infected aortic aneurysm, and tissue infiltration of IgG4-positive cell was later demonstrated in the surgical samples of aneurysmal wall.[10]

Inpatient case with the highest IgG4 levels

The patient who had the highest serum IgG4 level among inpatient group (InPt-case 1) was a 77-year-old man (**Table 2**). Four months prior to admission, prostate cancer was diagnosed histologically in this patient, and medi-

Table 2 Clinical diagnosis of cardiac inpatients with increased serum IgG4 concentrations

	IgG4, mg/dL	Age, years	Sex	Cardiovascular disease	Accompanying conditions
InPt-case 1	1240	77	M	Orthostatic hypotension	Prostate cancer
InPt-case 2	830	46	M	Cardiac dysfunction	Eosinophilic granulomatosis with polyangitis
InPt-case 3	564	67	M	Ischemic heart disease	
InPt-case 4	387	75	F	Suspected ischemic heart disease	
InPt-case 5	331	75	F	Heart failure	Lung cancer
InPt-case 6	331	62	M	Arteriosclerosis obliterans	
InPt-case 7*	366	67	M	Suspected infected aortic aneurysm	
InPt-case 8	204	60	M	Congestive heart failure	History of influenza associated myocarditis
InPt-case 9	187	74	M	Abdominal aortic aneurysm, silent myocardial ischemia	
InPt-case 10	184	71	M	After coronary stent implantation	Maxillar cyst, post operation
InPt-case 11	172	76	M	Aortic regurgitation	
InPt-case 12	165	75	M	Silent myocardial ischemia	Common iliac artery dissection
InPt-case 13	164	81	M	Effort angina pectoris	
InPt-case 14	162	81	M	Gait disturbance	Mikulicz disease
InPt-case 15	155	69	M	Arteriosclerosis obliterans	
InPt-case 16	154	56	M	Old myocardial infarction	
InPt-case 17	154	79	M	Worsening heart failure	
InPt-case 18	152	77	M	Ischemic heart disease	
InPt-case 19	151	88	M	After coronary stent implantation	Prostatomegaly
InPt-case 20	144	59	M	Ischemic heart disease	
InPt-case 21	142	65	M	Congestive heart failure, old myocardial infarction, atrial fibrillation	
InPt-case 22	141	51	M	Unstable angina pectoris	
InPt-case 23	139	78	M	After coronary stent implantation	

*InPt-case 7 is the same patient as CT-case 5 in **Table 4**.

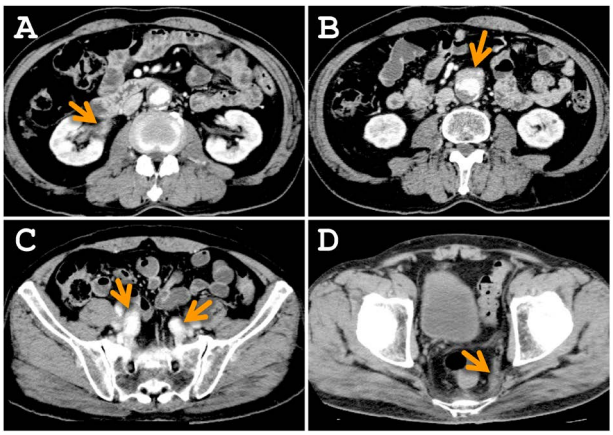

Fig. 3 Computed tomography images of cardiac inpatients who showed the highest serum IgG4 level among this group (InPt-case 1).
Arrows were indicated that soft tissue mass surrounding the right ureteropelvic junction (**A**), abdominal aorta (**B**), iliac arteries (**C**) and at the pelvic floor (**D**).

cal therapy (leuprorelin acetate and bicalutamide) was started. Thereafter, he started to feel dizziness that may be caused by orthostatic hypotension, and was admitted to our department. Abdominal CT revealed a soft tissue mass near the right ureteropelvic junction (**Fig. 3A**), around the iliac arteries and abdominal aorta (**Figs. 3B** and **3C**), and at the pelvic floor (**Fig. 3D**). Although they might be IgG4-related lesions, definitive diagnosis of IgG4-RD could not be made, because tissue samples were not available. There were no other lesions suspected of IgG4-RD, including pancreas. Serum TP and Alb levels were 9.2 mg/L and 3.8 mg/dL, respectively, and an A/G ratio was 0.70. White blood cell count was 8,470/μL with an eosinophil fraction of 8.4% (eosinophil count, 711/μL), thus eosinophilia was present. The underlying cause of orthostatic hypotension remained unidentified. The patient was treated with elastic stocking wear.

Clinical features of patients who underwent ECG-gated CT

Clinical features and serum IgG4 levels of patients

Table 3 demonstrates clinical features of patients in CT group. Although the most frequent reason for undergoing ECG-gated CT was to diagnose or follow-up coronary artery lesions, to acquire the left atrium images was another reason in patients with atrial fibrillation. The median IgG4 level was 43.7 mg/dL (IQR, 28.6–73.1 mg/dL) in men, which was significantly higher than that in women (32.2 mg/dL, IQR, 19.4–53.4 mg/dL, $P<0.001$, Mann–Whitney test). In CT group, a weak yet significant positive correlation was observed between age and IgG4 levels ($r=0.11$, $P=0.030$, Spearman's test).

Figure 2B presents the distribution of serum IgG4 levels among the 401 patients who underwent ECG-gated CT. Elevated level of serum IgG4 (≥135 mg/dL) was found in 17 patients (4.2%), and no significant difference in the proportion of elevated serum IgG4 levels was noted between women (5/163 [3.1%]) and men (12/238 [5.5%], $P=0.451$). In the CT group, no patients had a prior diagnosis of IgG4-RD. The reason for undergoing CT and accompanying conditions in 14 patients with high IgG4 levels (≥135 mg/dL) are described in **Table 4**. Case no. 5 of CT group (CT-case 5) is the same patient as InPt-case 7.[10]

Table 3 Characteristic of patients who underwent EGC-gated computed tomography

No. of subjects	401
Age, years	67.2±10.8
Women, n (%)	163 (40.6)
BMI, kg/m^2 (n=381)	23.7±3.6
Chronic hemodialysis, n (%)	11 (2.7)
Smoking status (n=335)	
Never (%)	213 (63.6)
Former/current (%)	122 (36.4)
Laboratory data	
White blood cell count, ×10^3/μL (n=379)	5.9±1.7
Hemoglobin, g/dL (n=380)	13.7±2.3
Platelet count, ×10^4/μL (n=380)	22.1±7.4
Total protein, g/dL (n=401)	7.1±0.5
Albumin, g/dL (n=401)	4.1±0.4
IgG4, (IQR) mg/dL	38.7 (24.8–62.9)
Creatinine*, mg/dL (n=390)	0.84±0.42
eGFR*, mL/min/1.73 m^2 (n=390)	68.4±16.9

*Excluding those with hemodialysis.
Data are presented as the mean±standard deviation or the median and interquartile range (IQR).

ECG-gated CT case with the highest IgG4 levels

The patient who showed highest serum IgG4 levels in this group (CT-case 1) was a 78-year-old man (**Table 4**). Five months prior to the CT examination, the patient underwent surgery for advanced gastric cancer. Detailed cardiovascular check-up, including coronary artery evaluation, was performed to identify the reason for sycope. Abdominal CT revealed a soft tissue mass encasing the abdominal aorta, common iliac artery, and internal iliac artery (marked perivascular thickening; **Figs. 4A–4C**). ECG-gated CT revealed no significant stenosis or periarterial thickening in the coronary artery (**Figs. 4D–4F**). No abnormal findings were found in the pancreas.

Laboratory data from this patient showed a TP of 7.6 mg/L, Alb of 3.3 mg/dL, and a A/G ratio of 0.77. The white blood cell count was 8,310/μL with the eosinophil fraction of 4.5%. The patient is undergoing periodic radiological follow-up without corticosteroid therapy. Similar degree of periarterial thickening was observed in CT images that was taken approximately 4 years later.

Table 4 Clinical diagnosis of patients undergoing EGC-gated computed tomography with increased serum IgG4 concentrations

	IgG4, mg/dL	Age, years	Sex	Cardiovascular disease	Accompanying conditions
CT-case 1	877	78	M	Syncope	Gastric cancer, post operation
CT-case 2	317	70	M	Paroxysmal atrial fibrillation	
CT-case 3	215	68	M	Ischemic heart disease	Suspected intraductal papillary mucinous neoplasm of the pancreas
CT-case 4	197	75	F	Suspected angina pectoris	Gastric carcinoid, post operation
CT-case 5*	193	67	M	Suspected infected aortic aneurysm	
CT-case 6	188	65	M	Congestive heart failure	Mediastinal lymphadenopathy
CT-case 7	185	77	M	Dilatation of the ascending aorta	Mediastinal lymphadenopathy
CT-case 8	168	70	F	Suspected angina pectoris	
CT-case 9	164	78	F	Dizziness	Mediastinal tumor
CT-case 10	162	81	F	Suspected angina pectoris	Lung cancer
CT-case 11	158	73	M	Suspected angina pectoris	
CT-case 12	152	72	M	Suspected silent myocardial ischemia	
CT-case 13	149	73	M	Suspected angina pectoris, pulmonary artery thrombosis	
CT-case 14	141	72	F	Suspected angina pectoris	Idiopathic thrombocytopenic purpura
CT-case 15	138	62	M	Suspected angina pectoris	
CT-case 16	138	74	M	Atrial fibrillation	
CT-case 17	135	80	M	Atrial fibrillation	

*CT-case 5 is the same patient as InPt-case 7 in **Table 2**.

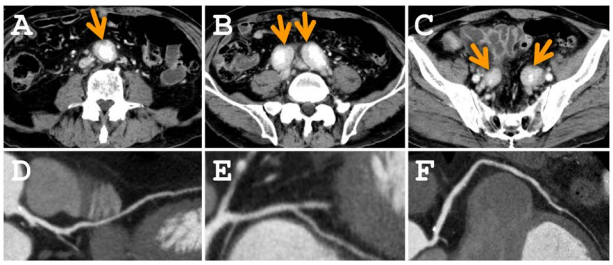

Fig. 4 Computed tomography images of the patient undergoing ECG-gated computed tomography who showed the highest serum IgG4 level among this group (CT-case 1).
Soft tissue mass encasing the abdominal aorta, and iliac and femoral arteries (**A**–**C**, arrows). Coronary arteries were normal (**D**–**F**).

Discussion

In the current study, we comprehensively measured serum IgG4 levels, after obtaining written informed consent, in 477 patients who were admitted to cardiology department and in 401 patients who underwent ECG-gated CT. Twenty-three (4.8%) subjects of 477 inpatient group and 17 (4.2%) of 401 CT group were found to have IgG4 levels ≥135 mg/dL. Examination of the medical records of those patients revealed that one of these patients had been diagnosed with Mikulicz disease (InPt-case 14) and another with IgG4-related coronary periarteritis (InPt-case 3), but IgG4-RD had not previously been diagnosed or suspected except these two cases. Radiologic images of patients who had the highest serum IgG4 levels in the inpatient group and CT group demonstrated a soft tissue mass encasing the arteries (marked periarterial thickening; **Figs. 3** and **4**) suggestive of IgG4-RD; however, due to the lack of tissue samples, a definite diagnosis of IgG4-RD could not be made.

It was found that patients with elevated IgG4 levels had relatively low A/G ratios. Serum IgG4 level had significantly negative correlation with A/G ratio even when patients who had low serum albumin level (<3.9 mg/dL) were excluded from the analysis. Although those with low A/G ratio (<1.0) were more likely to have higher serum IgG4 levels, the A/G ratio was >1.0 in the case who had been diagnosed with IgG4-related coronary periarteritis (InPt-case 3) in which serum IgG4 was 564 mg/dL; therefore, the A/G ratio of >1.0 may not be able to completely rule out the high serum IgG4 levels or possibility of IgG4-RD. A/G ratio may be affected by various factors, such as malnutrition, but the clinical importance of A/G ratio for diagnosing/suspecting elevated IgG4 should be analyzed in future studies.

In general, IgG4-RD is not a life-threatening disease, however, its involvement of cardiovascular system can sometimes be fatal, through the rupture of vascular wall. In addition, possibility exists that corticosteroid therapy, which is effective controlling the activity of IgG4-RD, might decrease the thickness of perivascular tissue and promote the fragilization of the vascular wall. IgG4-related cardiovascular lesion should be treated with particular

caution,[11,12] although proper diagnosis of IgG4-related cardiovascular lesions may be more difficult than IgG4-RD that affects other organs.

In the comprehensive diagnostic criteria (CDC) of IgG4-RD, definitive diagnosis requires the presence of fibro-inflammatory tissue thickening, elevated serum IgG4 levels, and the histopathological proof of IgG4-positive plasma cell infiltration.[13] However, tissue sampling from the heart and/or large vessels carries considerable risks, even if not impossible. Therefore, using only CDC may result in the under-diagnosis of IgG4-related cardiovascular disease.

In addition to CDC, there is so-called "organ-specific diagnostic criteria" in some non-cardiovascular organs, such as the pancreas and lachrymal and salivary glands. The organ-specific criteria may enable a definitive diagnosis even when histopathological assessment is not present,[14,15] because the radiologic image may present characteristic findings of IgG4-RD. On the other hand, IgG4-related cardiovascular disease does not demonstrate specific radiologic findings.[16] Therefore, a definitive diagnosis of IgG4-related cardiovascular disease cannot be made only from radiologic findings without histopathologic finding or accompanying definitively diagnosed IgG4-RD in non-cardiovascular organs. To which extent the elevated serum IgG4 levels ($\geq$135 mg/dL) support that possibility of IgG4-related cardiovascular disease has not been clear.

Hamano et al. reported that using an IgG4 cut-off level of $\geq$135 mg/dL, they could differentiate autoimmune pancreatitis, which is an IgG4-RD, from other pancreatic diseases with a sensitivity of 95% and specificity of 97%.[1] In the present study, in both inpatient group and CT group, serum IgG4 levels $\geq$135 mg/dL was observed in more than 4% of the subjects, but IgG4-RD had not been diagnosed in most of these cases. Therefore, exceeding serum IgG4 cut-off value of 135 mg/dL is not an exclusive finding in IgG4-related cardiovascular disease. Periarterial thickening, a radiologic finding of IgG4-related periaortitis/periarteritis, is often resemble that observed in other diseases or conditions, such as atherosclerosis. Considering that atherosclerotic vascular changes are frequently observed among cardiology patients, taking the elevation of serum IgG4 levels as the diagnostic ground among them may lead to overdiagnosis of IgG4-related vascular disease.

It may be questioned what would be the clinical importance in making the diagnosis of IgG4-related cardiovascular disease. We still cannot fully answer this question, but there are several possibilities. First, the popularization of the concept of IgG4-RD has led to an increase in the number of patients diagnosed with IgG4-RD of various organs. As IgG4-RD can either synchronously or metachronously appear in various organs throughout the body; therefore, IgG4-related vascular lesions may emerge during the clinical course of patients with IgG4-RD in non-vascular organs.[17] In fact, we encountered a patient with autoimmune pancreatitis, who developed IgG4-related coronary periarteritis/aneurysm and required coronary artery bypass surgery.[18] Second, in reverse, in cases in which heart and vessels are the index organs for the diagnosis of IgG4-RD, we can anticipate the possible emergence of IgG4-RD in other organs, and plan to perform appropriate systemic search. Third, as incidence of malignant disorder is reported to be higher in patients with IgG4-RD,[19] diagnosis of IgG4-RD may make us aware of the necessity of careful exclusion of malignant disease. Fourth, although corticosteroid therapy is generally effective in controlling the activity of IgG4-RD, it might promote fragilization of vessel wall of IgG4-related vascular disease, leading to the expansion and rupture of the vessels.[11] Finally, in Japan, IgG4-RD has been designated as an intractable disease, thus, proper diagnosis and appropriate treatment for cardiovascular involvement of IgG4-RD is needed.

Conclusion

We comprehensively measured serum IgG4 levels in 477 patients who were admitted to the cardiology department and in 401 patients who underwent ECG-gated CT. It was found that 23 patients (4.8%) in inpatient group and 14 patients (4.2%) in CT group had serum IgG4 levels $\geq$135 mg/dL. On the other hand, only in two patients with high serum IgG4 level were found to have been diagnosed with IgG4-RD. Histopathological assessment of cardiovascular tissue for the diagnosis of IgG4-RD is often difficult due to the potential risk of tissue sampling. In addition, there are no specific radiologic findings of IgG4-related cardiovascular disease, high serum IgG4 level ($\geqq$135 mg/dL) alone may not provide sufficient grounds for the diagnosis of IgG4-cardiovascular disease, because serum IgG4 level $\geq$135 mg/dL can be observed in more than 4% in cardiology patients. To avoid over-diagnosis and inappropriate treatment, diagnosis of IgG4-related cardiovascular disease should carefully be made especially when histopathologic analysis of cardiovascular tissue is not available.

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Disclosure Statement

The authors have no conflicts of interest to disclose with regard to the present study.

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