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Review

Characteristics and prognosis of IgG4-related periaortitis/periarteritis: A systematic literature review

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ABSTRACT

Objective: Immunoglobulin G4 (IgG4)-related disease is a systemic chronic fibroinflammatory disease that can affect almost every organ of the body. IgG4-related periaortitis/periarteritis is a newly recognized subset of IgG4-related disease, and its characteristics and prognosis remain unclear. We investigated the clinical characteristics and prognosis of IgG4-related periaortitis/periarteritis.

Methods: We performed a systematic literature review of IgG4-related periaortitis/periarteritis. Additionally, we have summarized the characteristics and prognosis of IgG4-related coronary arteritis.

Results: We investigated 248 patients with IgG4-related periaortitis/periarteritis. All studies reported the condition in elderly patients, and male predominance was observed. The infra-renal abdominal aorta and iliac arteries were the most commonly affected sites. Most reports showed the serum C-reactive protein elevation in this disease entity, in contrast to non-vascular IgG4-related disease. Based on radiological findings observed in 27 patients with IgG4-related coronary arteritis, vasculitic lesions were classified into 3 types: stenotic (67% of patients), aneurysmal (42%), and diffuse wall thickening type (92%). Serum IgG4 level, but not C-reactive protein level, was associated with the number of affected organs in IgG4-related coronary arteritis. Corticosteroid treatment with or without cardiac surgery or percutaneous coronary intervention was effective in most patients with IgG4-related coronary arteritis; however, 33% of patients showed an unfavorable clinical course including disease progression, relapse, or death. Pre-treatment stenosis and/or aneurysms were associated with progression of stenosis or aneurysm after corticosteroid treatment.

Conclusion: Most clinical characteristics were similar between the IgG4-related periaortitis/periarteritis and the non-vascular IgG4-related disease groups; however, serum C-reactive protein level elevation was observed only in the former. Although corticosteroid treatment was effective, this disease can be life-threatening secondary to myocardial infarction, aortic dissection, and aneurysmal rupture. Pre-treatment evaluation of stenosis or aneurysms is important for predicting progression of stenosis or aneurysm after corticosteroid treatment.

1. Introduction

Immunoglobulin G4 (IgG4)-related disease is a chronic fibroinflammatory disease characterized by serum IgG4 elevation, as well as histopathological changes including massive infiltration of IgG4-positive plasma cells at the affected sites and storiform fibrosis [1,2]. Recent advances in understanding the pathogenesis of this disease reveal the role of disease-associated T cell subsets and innate immune responses such as T-follicular helper cells [3–6], cytotoxic CD4 T cells [7], T helper type 2 and regulatory T cells [8,9], plasmablasts [10], and alternatively activated macrophages [11,12].

Various organs such as the orbits, lacrimal and salivary glands, the lungs, pancreas, the biliary tract, kidneys, retroperitoneum, mediastinal tissue, as well as lymph nodes and blood vessels are affected [1,2,13,14]. In untreated cases, the affected organs become dysfunctional secondary to enlargement and severe fibrosis. Despite the introduction of B-cell depletion therapy as a promising approach, corticosteroids remain the mainstay of therapy [2]. The high rates of relapse during corticosteroid tapering [16] and various adverse effects associated with prolonged corticosteroid use are problematic. Comorbidities and polypharmacy in elderly patients, who are predisposed to this disease, tend to exaggerate this risk.

Periaortitis or periarteritis is a critical clinical manifestation of IgG4-related disease that occurs in 10%–30% of patients [17], and may present as an isolated manifestation or as a component of systemic organ involvement. The 2012 revised International Chapel Hill

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Consensus Conference Nomenclature on Vasculitides proposed IgG4-related disease as a potential cause of aortitis [18]. This condition affects not only the aorta but also medium-sized arteries, such as the coronary, carotid, pulmonary, splenic, mesenteric and iliac arteries [17]. IgG4-related periaortitis/periarteritis can cause life-threatening complications such as aortic aneurysm rupture and arterial stenosis; however, details of the clinical characteristics, prognosis, and optimal treatment remain unclear owing to the rarity of this condition.

In this study, we reviewed the published literature describing IgG4-related periaortitis/periarteritis and summarized the clinical characteristics and prognosis of this disease.

2. Materials and methods

We performed a careful search of the literature published in English in the PubMed database using the following Medical Subject Heading terms: “IgG4-related periaortitis”, “IgG4-related periarteritis”, “IgG4-related inflammatory aortic aneurysm”, “IgG4-related coronary artery”, or “IgG4-related coronary arteritis” from the inception dates until March 27, 2019. Two investigators (MA and YK) independently screened the identified articles based on their relevance to the topic. Disagreements were resolved by consensus through discussions. Each article identified in the literature was carefully reviewed, and we only included articles that enrolled patients aged ≥18 years in whom the diagnosis was based on comprehensive classification criteria [19]. Articles not describing IgG4-related periaortitis/periarteritis or coronary arteritis, those lacking important clinical information including age, sex, and serum IgG4 levels, or histopathological confirmation of diagnosis, basic research articles, and review articles were excluded. All identified articles were classified into an IgG4-related periaortitis/periarteritis and a coronary arteritis group. Single case reports describing IgG4-related periaortitis/periarteritis were excluded; however, single case reports describing IgG4-related coronary arteritis were included because this condition is being increasingly recognized as a life-threatening disease that, to date, has been reported only in case reports. This systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Ethical approval was not necessary for this study because we used existing data.

3. Results

3.1. Literature search

We initially identified 142 potentially relevant articles of which 108 were excluded based on the aforementioned inclusion/exclusion criteria (5 non-English articles, 30 unrelated to IgG4-related periaortitis/periarteritis or coronary arteritis, 20 with insufficient clinical information, 17 single case reports describing periaortitis, 7 basic research articles, and 29 reviews). Eventually, 7 articles were included in the study for IgG4-related periaortitis/periarteritis, 24 articles for IgG4-related coronary arteritis, and 3 articles for both conditions.

3.2. Characteristics and prognosis of immunoglobulin G4-related periaortitis/periarteritis

We identified 10 articles that described 248 patients with IgG4-related periaortitis/periarteritis (Table 1) [20–29]. Demographics showed that elderly patients (age range 52–81 years, mean or median) were most commonly affected, and male predominance (60–100%) was observed. These findings were similar to the age and sex predominance associated with non-vascular IgG4-related disease [2]. The percentage of patients presenting with only periaortitis/periarteritis was 10–30%. The infra-renal abdominal aorta and iliac arteries were the most commonly affected sites identified in all studies (52–100%). Aneurysmal change, which is occasionally life-threatening, occurred in 8–100% of

Table 1
Patient demographics of IgG4-related periaortitis/periarteritis.

Author (year)	Number of patients	Age, years	Male, *n* (%)	Isolated type, *n* (%)	Infra-renal abdominal aorta and iliac arteries, *n* (%)	Aneurysmal change, *n* (%)	Allergic history, *n* (%)
Qi L et al. (2019)	21	52 (mean)	15 (71%)	2 (10%)	11 (52%)	10 (48%)	NA
Kasashima S et al. (2018)	32	IgG4-AA: 81 (median) IgG4-PA: 77 (median)	26 (81%)	NA	NA	24 (75%)	NA
Ozawa M et al. (2017)	65	69 (median)	53 (82%)	NA	53 (82%)	8 (19%)	17 (26%)
Kim IY et al. (2017)	10	69 (median)	6 (60%)	3 (30%)	7 (70%)	3 (30%)	NA
Yabusaki S et al. (2017)	15	70 (median)	12 (80%)	0 (0%)	14 (93%)	10 (67%)	NA
Perugino CA et al. (2016)	36	59 (median)	28 (78%)	2 (6%)	23 (64%)	11 (31%)	NA
Castelein T et al. (2015)	9	61 (median)	9 (100%)	1 (1%)	6 (67%)	NA	NA
Ebe H et al. (2015)	7	66.9 (mean)	6 (86%)	1 (14%)	6 (86%)	NA	NA
Mizushima et al. (2014)	40	66 (mean)	37 (93%)	4 (10%)	40 (100%)	3 (8%)	NA
Kasashima S et al. (2009)	13	70 (median)	11 (85%)	NA	NA	13 (100%)	5 (38%)

NA: not available.

Table 2
Laboratory findings of IgG4-related periaortitis/periarteritis.

Author (year)	Serum IgG4 level, mg/dL	Serum IgE level, IU/mL	Serum CRP level, mg/dL	Elevated serum CRP, *n* (%)
Qi L et al. (2019)	433 (median)	NA	0.33 (mean)	NA
Kasashima S et al. (2018)	IgG4-AA: 254 (median) IgG4-PA: 282 (median)	NA	IgG4-AA: 1.86 (median) IgG4-PA: 2.15 (median)	IgG4-AA: 13 (54%) IgG4-PA: 6 (75%)
Ozawa M et al. (2017)	511 (median)	172 (median)	0.17 (median)	NA
Kim IY et al. (2017)	193 (median)	212 (median)	1.42 (median)	9 (90%)
Yabusaki S et al. (2017)	768 (median)	NA	NA	NA
Perugino CA et al. (2016)	99 (median)	NA	1.55 (median)	26 (87%)
Castelein T et al. (2015)	511 (mean)	NA	3.06 (median)	NA
Ebe H et al. (2015)	933 (mean)	NA	1.42 (mean)	2 (29%)
Mizushima I et al. (2014)	815 (mean)	403 (mean)	0.56 (mean)	18 (45%)
Kasashima S et al. (2009)	274 (mean)	1124 (mean)	2.60 (mean)	NA

NA; not available.

patients. Aortic dissection was reported in only 1 patient, and stenosis was not reported (observed in cases with IgG4-related coronary arteritis or IgG4-related pulmonary arteritis) [25]. Most studies did not investigate the association of this condition with a history of allergies; however, 2 studies reported a history of allergies in 26% and 38% of patients.

Laboratory findings are summarized in Table 2. The mean or median serum IgG4 levels ranged from 99 to 933 mg/dL. In 4 studies, the mean or median serum IgE levels ranged from 172 to 1124 IU/mL. Serum C-reactive protein were elevated in patients with IgG4-related periaortitis/periarteritis (mean or median 0.17–3.06 mg/dL), in contrast to non-vascular IgG4-related diseases such as Mikulicz disease [30,31]. Elevated serum C-reactive protein levels were observed in 29–90% of patients.

Kasashima et al. [29] investigated the histopathological features of IgG4-related periaortitis/periarteritis. In addition to the common histopathological characteristics of IgG4-related disease such as massive infiltration of IgG4-positive plasma cells and fibrosis, the authors identified significant adventitial thickening (but no intimal thickening) and the massive emergence of adventitial tertiary lymphoid organs in all patients, as well as the infiltration of eosinophils in 85% of patients. Neutrophils were essentially absent.

Six studies reported treatment response in patients with IgG4-related periaortitis/periarteritis, as shown in Table 3. All studies reported that patients showed a good response to treatment with primarily corticosteroids. However, several reports described aneurysm progression after corticosteroid treatment. Two studies [22,28] reported that pre-treatment occurrence of aneurysm was associated with aneurysm progression after corticosteroid treatment. Long-term prognosis remained unclear.

3.3. Characteristics and prognosis of immunoglobulin G4-related coronary arteritis

We identified 27 articles that described 27 patients with IgG4-related coronary arteritis [20,25,27,32–55] (Table 4). The mean age was 66 years and 81% were men. The mean serum IgG4 and IgE levels were 1238 mg/dL and 2634 IU/mL, respectively. Serum C-reactive protein levels were also elevated (mean 2.95 mg/dL [normal value < 0.3 mg/dL]). Among the patients in whom serum C-reactive protein levels were available, 64% ($n = 14$) showed elevated values.

Based on radiological findings observed in coronary arteries, vasculitic lesions were classified into 3 types as follows: stenotic, aneurysmal, and diffuse wall thickening types (Fig. 1a). As shown in Fig. 1b, stenosis was identified in 67%, aneurysms in 42%, and diffuse wall thickening in 92% of patients. Notably, 22% of patients showed all 3 types of lesions (Fig. 1b). Most patients showed multiple coronary lesions, and concomitant pericardial lesions were observed in 2 patients.

Other organs were involved in 59% (16/27) of patients. The mean number of affected organs was 2. We reported in our previous study that higher serum IgG4 levels reflected multiorgan involvement [15]. Similar to our findings, we found a positive correlation between serum IgG4 levels and the number of affected organs in patients with IgG4-related coronary arteritis [20,25,27,32–47,49–55]. However, serum C-reactive protein levels were not correlated with the number of affected organs [25,27,33–35,39,40,45,49,51,53] (Fig. 2).

Corticosteroid treatment with or without cardiac surgery or percutaneous coronary intervention was effective in most cases. However, 1 patient (4%) relapsed during corticosteroid tapering, 4 patients (15%) showed progression of coronary artery stenosis or aneurysm despite treatment, and 4 patients (15%) died (1 patient with myocardial infarction, 1 with splenic aneurysm rupture, 1 with thoracic aortic aneurysm rupture, and 1 with sepsis). Thus, 9 patients (33%) with IgG4-

Table 3
Response to treatment.

Author (year)	Treatment	Observation period	Prognosis
Qi L et al. (2019)	Corticosteroid	10 months (median)	All 13 patients showed improvement of wall thickening, but 2 patients also exhibited worsening of luminal dilatation.
Ozawa M et al. (2017)	Corticosteroid	NA	All 43 patients showed improvement of wall thickening, but 9 patients also exhibited worsening of luminal dilatation.
Kim IY et al. (2017)	Corticosteroid	Over 6 months	7 patients showed improvement of wall thickening, but 3 patients showed persistent wall thickening.
Perugino CA et al. (2016)	Corticosteroid, rituximab, surgery	NA	All patients showed clinical improvement.
Ebe H et al. (2015)	Corticosteroid	3–6 months	All 6 patients showed improvement of wall thickening.
Mizushima I et al. (2014)	Corticosteroid	30 months (mean)	30 patients showed improvement of wall thickening, but 1 patients showed relapse during corticosteroid tapering. Among 4 patients with luminal dilatation before therapy, 2 showed exacerbations of luminal dilatation after therapy. On the other hand, none of the patients without luminal dilatation showed a new appearance of luminal dilatation after therapy.

NA: not available.

Table 4
Clinical characteristics of IgG4-related coronary periarteritis.

Author (year)	Age, years	Sex	Stenotic change	Aneurysmal change	Thickening of the wall	Other organ involvement	Number of affected organs	Serum IgG4 level, mg/dL	Serum IgE level, IU/mL	Serum CRP level, mg/dL	Treatment and outcome
Qi L et al. (2019)	69	M	+	−	+	Pancreas	2	371	NA	NA	Corticosteroid improved the clinical manifestations.
Ruggio A et al. (2018)	65	M	+	+	+	Dacryoadenitis, parotid glands, skin, lymph nodes	5	2607	NA	NA	Myocardial infarction was treated with steroid, antiplatelet and oral anticoagulation therapy and maintained stable.
Matsuda J et al. (2018)	70	F	−	−	+	Dacryoadenitis, retroperitoneal fibrosis, pancreas, right common iliac artery	4	758	NA	1.06	Steroid treatment improved all clinical manifestation.
Komiya Y et al. (2018)	59	M	−	−	+	Abdominal aortic aneurysm, submandibular and parotid glands, lymph nodes	4	2929	NA	0.18	Steroid treatment improved clinical manifestation without relapse for 3 years.
Sakamoto A et al. (2017)	67	M	+	−	+	Pancreas	2	231	NA	2.07	Coronary CT angiography showed a resolution of the coronary stenosis and the wall thickness after 4 months of steroid treatment. But coronary periarteritis relapsed when steroid dose was tapered to 5 mg/day.
Barbu M et al. (2017)	55	F	+	−	+	Thoracic aorta	1	330	NA	NA	Surgery and immunosuppressive treatment (glucocorticoids, rituximab, and methotrexate) were conducted, but the detail of follow-up was not noted.
Ibrahim T et al. (2017)	70	M	−	−	+	Thoracic aorta, abdominal aortic aneurysm, iliac arteries and orbital pseudotumor	2	3030	NA	NA	Corticosteroid and rituximab were initiated. Three months later, the patient died of urosepsis and pseudomembranous colitis.
Kanzaki Y et al. (2017)	66	M	+	−	+	−	1	564	NA	NA	The patient underwent coronary bypass surgery, followed by percutaneous coronary intervention, which improved clinical symptoms. The disease is stable for 5 years without corticosteroid treatment, although the FDG-uptake is observed in the lesions.
Hourai R et al. (2016)	75	M	+	−	+	Abdominal aorta, pericardium, lymph node	3	625	359	1.05	Corticosteroid effectively improved the pleural fluid.
Nishimura S et al. (2016)	60	M	+	+	−	Thoracic aorta, salivary gland, pancreas	3	1350	1500	0.2	Balloon angioplasty without steroid exacerbated aneurysms and stenosis. Steroid treatment considerably improved blood flow and did not exacerbate aneurysms.
Perugino CA et al. (2016)	52	M	+	+	+	Pericardium, kidney, abdominal aorta, iliac artery, and superior mesenteric artery	3	1980	NA	9.5	Rituximab improved the vessel involvement, but the end-stage renal disease was not improved.
Delgado-García G et al. (2016)	44	F	+	−	+	Lymph node	2	99.7	NA	normal	Surgery and rituximab treatment were performed. Three months later, disease remained clinically inactive.
Higashi H et al. (2016)	67	M	+	−	+	Infra-renal aorta	1	197	NA	NA	Balloon angioplasty and corticosteroid treatment improved clinical manifestations.
Ito S et al. (2016)	76	F	+	−	+	−	1	261	NA	NA	Percutaneous coronary intervention relieved the symptoms.
Hamanaka K et al. (2015)	57	M	−	−	+	−	1	356	NA	NA	NA
Kusunose K et al. (2015)	80	M	−	+	+	Lacrimal gland, ascending aorta, subclavian and iliac arteries	2	1210	NA	7.08	Because of the risk of cardiac surgery, this case was treated with only corticosteroid, which improved clinical manifestations.
Kan-o M et al. (2015)	68	M	+	+	+	Infrarenal abdominal aortic aneurysm, liac arteries, pancreas, kidney and lymph nodes	4	1360	NA	Normal	After surgery for abdominal aortic aneurysms, corticosteroid was initiated and improved the coronary artery lesions 4 months later.

(*continued on next page*)

Table 4 (*continued*)

Author (year)	Age, years	Sex	Stenotic change	Aneurysmal change	Thickening of the wall	Other organ involvement	Number of affected organs	Serum IgG4 level, mg/dL	Serum IgE level, IU/mL	Serum CRP level, mg/dL	Treatment and outcome
Ebe H et al. (2015)	66	M	NA	NA	NA	Lymph nodes	2	323	NA	9.49	Corticosteroid improved clinical manifestations.
Bito Y et al. (2014)	69	M	−	+	−	−	1	161	NA	NA	Corticosteroid treatment was initiated, but aneurysmal change was exacerbated. Thus, surgery was performed.
Patel NR et al. (2014)	53	M	+	−	+	Kidneys, pancreas, and lymph nodes	4	NA	NA	NA	This case was presented as sudden death due to myocardial infarction.
Tajima M et al. (2013)	68	M	−	+	+	Carotid, subclavian, axillary, brachial, hepatic splenic, and iliac arteries, aorta, salivary glands, and lymph nodes	3	2390	9716	0.97	After 6 months of corticosteroid treatment, the patient died of splenic aneurysm rupture.
Urabe Y et al. (2012)	84	M	+	+	+	Submandibular glands, celiac artery, renal arteries, thoracic aorta	2	2630	NA	NA	Coronary artery stent was implanted. Corticosteroid was also initiated but the patient unexpectedly died of a ruptured thoracic aorta 3 months after the initial presentation.
Kusumoto S et al. (2012)	62	M	+	−	+	Infrarenal abdominal aorta	1	2170	681	0.43	Corticosteroid treatment markedly reduced the mass lesions of coronary artery and abdominal aorta. No relapse was observed at 1-yer follow-up.
Tanigawa J et al. (2012)	66	M	+	−	+	−	1	564	NA	NA	Bypass surgery was performed, however, the artery was occluded 1 year after surgery.
Takei H et al. (2012)	71	M	+	+	+	Abdominal aortic aneurysm, pancreas, submandibular and parotid glands	4	2720	913	0.4	Cyclophosphamide and corticosteroid were initiated and did not exacerbate vascular lesions for 2 years.
Ikutomi M et al. (2011)	75	M	+	+	+	Abdominal aortic aneurysm, pancreas, parotid glands	3	2510	NA	NA	Steroid treatment initially improved clinical manifestation, but during follow-up the right coronary artery was further dilated and the surrounding tumorous tissue enlarged, leading to surgical resection of the aneurysm and coronary artery bypass grafting.
Matsumoto Y et al. (2007)	63	F	−	+	+	Abdominal aortic aneurysm	1	456	NA	normal	Surgery without steroid therapy. No event was observed during 5 month follow-up.

NA: not available.

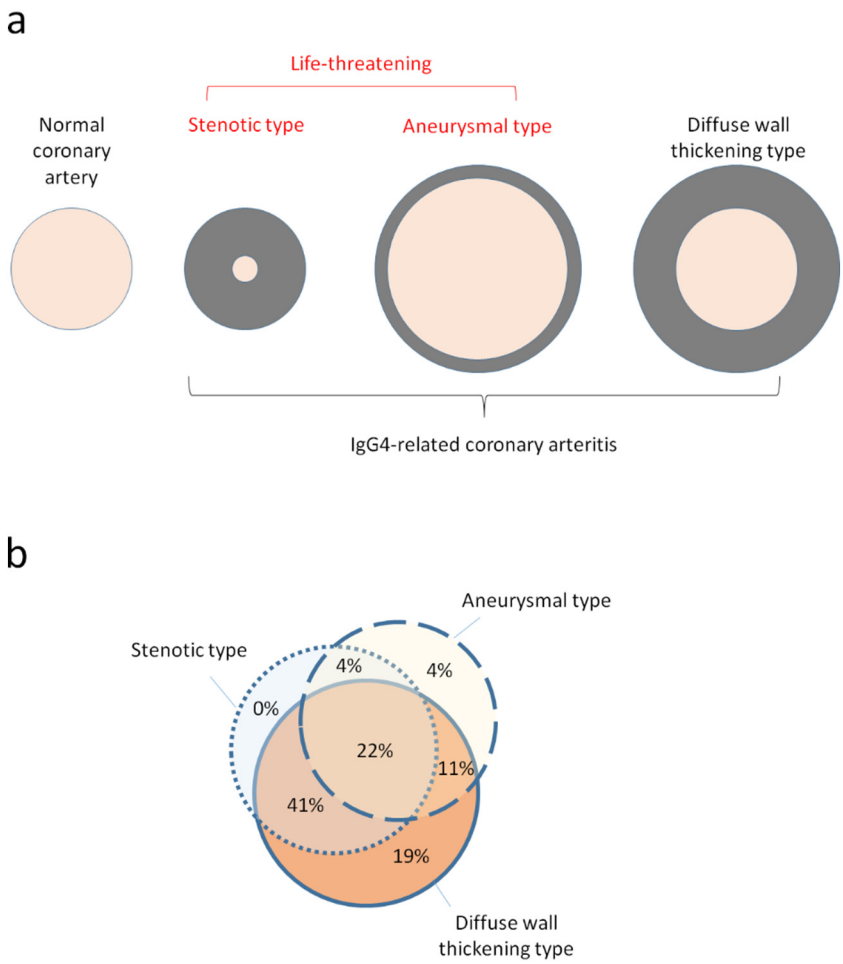

Fig. 1. The radiological classification of IgG4-related coronary arteritis (a) and their frequency (b).

related coronary arteritis showed an unfavorable clinical course. Notably, pre-treatment stenosis and/or aneurysms were present in all patients who developed progression of stenosis or aneurysm after treatment.

4. Discussion

In this study, we observed that the clinical characteristics of IgG4-related periaortitis/periarteritis or coronary arteritis were essentially similar to those observed in patients with non-vascular IgG4-related disease. However, serum C-reactive protein elevation was typically observed in patients with IgG4-related periaortitis/periarteritis in contrast to non-vascular IgG4-related disease. The infra-renal abdominal aorta and iliac arteries were the most commonly affected sites in patients with IgG4-related periaortitis/periarteritis. Based on radiological findings, vasculitic lesions in patients with IgG4-related coronary arteritis were classified as follows: stenotic, aneurysmal and diffuse wall thickening types. Although corticosteroid treatment was

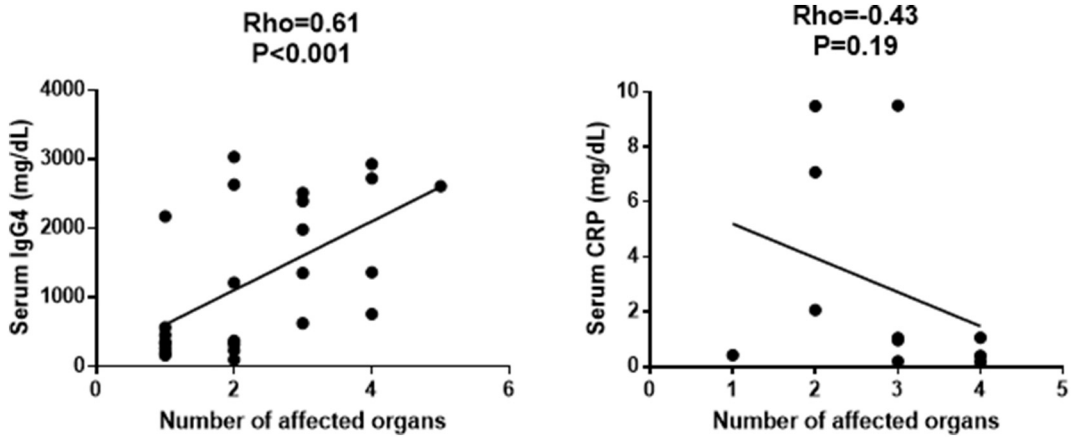

Fig. 2. The correlation between number of affected organs and serum IgG4 [20,25,27,32–47,49–55] or C-reactive protein levels [25,27,33–35,39,40,45,49,51,53] in IgG4-related coronary arteritis.

effective, a few patients developed unfavorable outcomes such as myocardial infarction, dissection, aneurysmal rupture, and even death.

IgG4-related disease is a relatively new disease entity that can affect various organs, including the lacrimal and salivary glands, the pancreas, kidney, lungs, lymph nodes, and blood vessels [2]. Although IgG4-related disease is characterized by elevated serum IgG4 levels and IgG4-positive plasma cell infiltration, it might present with heterogeneous subgroups with different underlying pathogenic mechanisms. Our present study highlights the clinical and pathogenic features of the IgG4-related periaortitis/periarteritis or coronary arteritis subgroup in which patients present with elevated serum C-reactive protein levels. This finding is important in determining the pathogenesis of this disease entity because previous studies have reported that non-vascular IgG4-related disease (involving the lacrimal and submandibular glands, the kidneys and/or lymph nodes) show normal serum C-reactive protein and interleukin-6 levels [30,31,56,57]. Kasashima S et al. recently reported that interleukin-6-positive cells were more commonly observed at the affected sites in patients with IgG4-related periaortitis/periarteritis than in patients with other types of IgG4-related disease [21].

Kasashima S et al. also observed that the elevated levels of Th2-type cytokine-expressing cells and the presence of tertiary lymphoid organs in affected lesions (common histopathological features observed in patients with IgG4-related disease), are characteristically prominent in patients with IgG4-related periaortitis/periarteritis [58]. Interestingly, Th2-type cytokines are not involved in the pathogenesis of other types of aortitis/arteritis, such as giant cell arteritis, which involve the action of Th1- and Th17-type cytokines [59–61]. Additionally, IgG4-related periaortitis/periarteritis primarily involves the adventitia with tertiary lymphoid organs formation in contrast to giant cell arteritis, which primarily involves the media causing intimal hyperplasia. Thus, to summarize, IgG4-related periaortitis/periarteritis differs from other autoimmune aortitis/arteritis and is unique among the IgG4-related disease entities in terms of inflammatory features such as elevated serum C-reactive protein levels. Compared with the other types of IgG4-related disease, the pathomechanism underlying exclusive IgG4-related periaortitis/periarteritis that presents with systemic inflammation is unclear, and future studies are warranted in this context.

We need to note that conditions that mimic IgG4-related periaortitis/periarteritis, such as anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), multicentric Castleman disease, lymphoma, and Rosai-Dorfman disease should be ruled out in patients with suspected IgG4-related periaortitis/periarteritis, because these conditions can also show a periaortitis/periarteritis-type presentation with elevated serum levels of IgG4 and C-reactive protein [30,62–68]. However, clinicians occasionally face with the difficulty to differentiate AAV from IgG4-related disease or vice versa, suggesting that AAV and IgG4-related disease might overlap. In fact, recent studies reported “a new overlap syndrome” which show clinical features of both AAV and IgG4-related disease [62,63]. Interestingly, chronic periaortitis was the main manifestation in AAV and IgG4-related disease overlap syndrome [63]. Clinicians need to think about the possible coexistence of AAV and IgG4-related disease when performing further workup. Coexistence of AAV and IgG4-related disease indicates the common pathogenic mechanisms between the two diseases such as the involvements of T follicular helper cells, cytotoxic T cells, and B cells [69,70], although further studies are required. Also, tertiary lymphoid organs are commonly observed at affected sites of both AAV and IgG4-related disease [70]. Rituximab can be the optimal treatment in AAV and IgG4-related disease overlap syndrome because rituximab is reported to be effective in both AAV [71] and IgG4-related disease [72].

Obtaining specimens from the aortic and coronary artery walls is challenging; therefore, noninvasive imaging is important for diagnostic evaluation and treatment of IgG4-related periaortitis/periarteritis or coronary arteritis. The current review showed that based on radiological findings of vasculitic lesions, patients with IgG4-related aortitis could be categorized as those with aneurysmal- and those with diffuse wall thickening-type disease. Similarly, patients with IgG4-related coronary arteritis could be classified as those with stenotic-, aneurysmal-, or diffuse wall thickening-type disease. Myocardial infarction and/or arterial rupture can be fatal; therefore, accurate evaluation of vascular involvement in IgG4-related disease using optimal imaging modalities is important for appropriate treatment planning (mechanical intervention vs. surgery vs. corticosteroid therapy).

Corticosteroid therapy is usually effective in patients with IgG4-related disease and early diagnosis is important for preventing irreversible organ damage [73]. However, up to 40% of patients tend to develop relapse within the first year of the corticosteroid taper [74], and long-term use of corticosteroid can precipitate toxicity. Additionally, patients with IgG4-related periaortitis/periarteritis, particularly those with coronary arteritis, can show unfavorable outcomes. Considering the role of systemic inflammation in IgG4-related periaortitis/periarteritis (indicated by increased serum C-reactive protein levels), interleukin-6 blockade is a candidate treatment for this disease entity [75,76]. Notably, several case reports have described the effectiveness of an anti-interleukin-6 receptor in patients with chronic periaortitis [77–79]. This treatment strategy for the distinctive IgG4-related disease clinical phenotypes requires further investigation [80]. In addition, since severe fibrosis is another important feature of IgG4-related disease, the treatments which were reported to be effective in other fibrotic conditions such as systemic sclerosis [81] may have potential benefits for IgG4-related disease.

IgG4-related periaortitis/periarteritis, as well as IgG4-related coronary arteritis are associated with the potential risk of aortic and arterial aneurysms. Our study highlighted a clinically important observation that patients with pre-treatment aneurysms showed a higher risk of aneurysm expansion and progression after corticosteroid treatment. Corticosteroid is a useful anti-inflammatory agent for the management of aneurysms; however, our findings suggest that corticosteroid may weaken the aneurysm wall, thereby increasing the risk of rupture in patients with pre-existing aneurysms. Thus a multidisciplinary approach to identify an optimal treatment strategy is warranted in such cases. Future studies should focus on identifying the optimal therapeutic strategy in patients with IgG4-related periaortitis/periarteritis and IgG4-related coronary arteritis.

5. Conclusion

Most clinical characteristics were similar between the IgG4-related periaortitis/periarteritis and the non-vascular IgG4-related disease groups, but serum C-reactive protein level elevation was unique only in the IgG4-related periaortitis/periarteritis. IgG4-related coronary arteritis was classified into 3 types: stenotic, aneurysmal, and diffuse wall thickening type. Although corticosteroid treatment was effective, this disease can be life-threatening secondary to myocardial infarction, aortic dissection, and aneurysmal rupture. Pre-treatment stenosis and/or aneurysms were the risk for progression of stenosis or aneurysm after corticosteroid treatment.

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Disclosure statement

The authors have no conflict of interest to declare.

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