

Invited critical review

IgG4-related disease underlying the pathogenesis of coronary artery disease

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ABSTRACT

Immunoglobulin G4 (IgG4)-related disease is a newly emerging clinicopathological entity that is characterized by increased serum IgG4 levels and tissue infiltration of IgG4-positive plasma cells. IgG4-related immune inflammation has been reported to be present in inflammatory aortic aneurysm, albeit not in every case. Several recent studies have suggested that IgG4-related disease may underlie certain coronary artery abnormalities, such as coronary aneurysm, pseudotumor, wall calcification, and intimal thickening. Here, what is known about IgG4-related coronary artery lesions, as well as questions that remain to be answered thus far, are discussed.

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1. Introduction

Recent studies have shown that immune and inflammatory reactions [1] and adventitial lymphocytic infiltration [2] may occur in atherosclerotic arteries, although how and whether T and B cell autoimmunity are related to the formation of coronary artery lesions remains to be fully elucidated. In vascular tissue, such immuno-inflammatory reactions are seen especially among a certain type of abdominal aortic aneurysm, designated “inflammatory aortic aneurysm” (IAAA), which accounts for 5–10% of all cases of aortic aneurysm. In IAAA, a thickening

of the aortic adventitia together with a marked infiltration of inflammatory cells (plasma cells, lymphocytes and macrophages) can be observed [3,4], suggesting the possible role of (auto)immunity in the development of aortic wall remodeling in this disorder. It has recently become evident that IAAA possesses, albeit not always, the clinicopathological feature of immunoglobulin G4 (IgG4)-related disease (IgG4-RD) [5].

IgG4-RD, a newly emerging clinicopathological entity, is characterized by the tumefaction or extensive tissue infiltration of IgG4-positive plasma cells and elevated concentrations serum IgG4 [6,7], which usually comprises only about 4% of total immunoglobulin G. IgG4-related histopathologies were first documented in autoimmune pancreatitis by Hamano et al. in 2001 [8], and subsequently it became apparent that IgG4-RD is a systemic disorder that may potentially

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involve a wide variety of organs including the lung, kidney, liver, and exocrinological and endocrinological organs [9–14]; as a result, IgG4-RD has been gathering increasing attention.

In addition to the abdominal aorta, IgG4-related histopathology features have been observed in the thoracic aorta [15] and smaller arteries (e.g. the iliac and superior mesenteric arteries) [16]. Information, however, seems to be limited regarding whether IgG4-RD might also affect the coronary arteries, a fact that might be due, in part, to the technical difficulty in obtaining coronary artery tissue for proving IgG4-positive cell infiltration around or within the coronary artery wall. Nevertheless, increasing evidence is indicating that IgG4-RD may target cardiovascular organs [17]. Herein I review recent articles to describe and discuss what is known thus far about IgG4-related coronary periarthritis.

2. Clinical pictures of IgG4-related coronary artery disease

2.1. Inflammatory pseudotumor and periarterial fibrosclerotic thickening

Inflammatory pseudotumor depicts a mass with a polymorphous inflammatory cell infiltrate, and variable amounts of fibrosis, necrosis, and granulomatous reaction. Malignant tumors, which are frequently suspected on initial presentation, should carefully be differentiated from this condition, as it is essentially a benign condition. Inflammatory pseudotumors can be found in almost all organ systems [18]. Recent studies have shown that inflammatory pseudotumors, albeit not all of them, possess clinicopathological features of IgG4-RD. In addition to the pancreas, IgG4-related inflammatory pseudotumors have been reported in the lung, liver, breast, central nervous system, orbit, paratestis, and trachea [19–25].

Inflammatory pseudotumors and/or periarterial fibrosclerotic thickening have been reported in the coronary artery. Matsumoto et al. reported an IgG4-related pseudotumor of the coronary artery in a 63-year-old patient who also had IAAA [26]. In this case, the size of the pseudotumor was huge (30 × 26 mm) and prominent IgG4-positive cell infiltrates were detected immunohistochemically in a surgically resected periarterial mass lesion. Serum IgG4 levels were found to be elevated to 456 mg/dL (normal range <135 mg/dL). Ikutomi et al. reported a 75-year-old man who had a history of autoimmune pancreatitis and was admitted with chest symptoms on exertion. In this case, tumorous fibrosclerosis was present diffusely around the coronary artery and was most prominent in the right coronary artery. On admission of the patient, increased abdominal aortic wall thickness was also noted. Ikutomi et al. performed 18F-fluorodeoxyglucose (FDG) positron-emission tomography (PET), which showed enhanced uptake of FDG in the coronary periarterial mass, submandibular glands, pancreas, and retroperitoneal regions [27], suggesting the presence of active IgG4-related immune inflammation in these regions [28,29]. In addition, Kusumoto et al. reported a 62-year-old man with IgG4-related fibrosclerotic mass lesions surrounding the coronary artery and abdominal aorta [30]. Coronary periarterial tissue samples that were obtained by a needle biopsy showed prominent IgG4-positive plasma cell infiltrates and fibrosclerotic thickening, leading to IgG4-related coronary periarthritis. This patient was treated with corticosteroid therapy, which reduced the size of the perivascular soft mass around the coronary artery and abdominal aorta.

Tanigawa et al. recently reported a 66-year-old man who presented with symptoms related to coronary ischemia. Invasive coronary angiography showed, along with significant coronary stenosis, feeding artery-like small diameter vessels near the stenotic site. Computed tomography coronary angiography, however, had to be used to confirm the presence of a coronary artery pseudotumor (Fig. 1) in this case. This pseudotumor was diagnosed to be IgG4-related histologically via biopsy samples that were obtained during the bypass surgery [31]. Tanigawa et al.'s patient did not undergo corticosteroid therapy after bypass surgery due to the possibility of enhanced thrombogenicity; however, serum

IgG4 concentration showed a transient decline, which returned to the pre-surgical level about 1 year after the operation, and, notably, the size of the periarterial mass was gradually decreased (Fig. 2) [32].

2.2. Coronary artery aneurysm

In IAAA, IgG4-related inflammation is considered to play a role in arterial wall remodeling (aneurysm). On the other hand, idiopathic retroperitoneal fibrosis, which is not accompanied by aortic aneurysm, is known to share common histopathological features with IAAA [33], and these two clinical entities may together be generically termed “chronic periaortitis” [34]. Notably, as in the case of IAAA, idiopathic retroperitoneal fibrosis is, albeit for a certain fraction, considered to be IgG4 related [35–37]. Thus, it might be asked whether IgG4-related inflammation is associated with coronary aneurysm. This question seems to have been answered positively. In the above-mentioned case of Ikutomi et al., coronary artery aneurysm was noted at the distal site of the right coronary artery (Fig. 3) [27]. In addition to this case, coronary artery (aneurysmal) dilatation, albeit much smaller, was also noted in the patient of Tanigawa et al. [31]. More recently, Urabe et al. reported a case of a 84-year-old man who was admitted with acute myocardial infarction which was caused by the intra-coronary thrombosis at the site of coronary aneurysm with the maximal diameter of 21 mm. CT angiography showed that most of the epicardial coronary arteries, including the left circumflex artery aneurysm, were diffusely and continuously surrounded by tumor-like lesions. The patient was died of a ruptured thoracic aorta, and prominent IgG4-positive plasma cell infiltrates in the coronary adventitia were proven histologically [38]. These observations suggest that IgG4-related immune inflammation may generate a coronary aneurysm.

For the management of patients with IAAA, both medical and surgical approaches may be taken, and corticosteroids and other immuno-suppressive drugs have been reported to be effective in controlling the disease activity [39]. It should be noted, however, that the ultimate efficacy of the anti-inflammatory approach has not been proven for IAAA [40], and coronary inflammatory aneurysm. Indeed, the coronary aneurysm was reported to increase in size over a short period of time irrespective of corticosteroid therapy in Ikutomi et al.'s case [27].

Coronary artery aneurysm is not an uncommon condition [41]; however, the percentage of involvement of IgG4-related pathology in coronary ectasia or aneurysm awaits further investigation.

2.3. Coronary artery stenosis

Unlike Takayasu's arteritis, another immune-mediated vascular inflammation [42], IgG4-related vascular inflammation takes place predominantly in the adventitial region [43]. Monocytic and lymphocytic infiltrates are observed in the intimal plaque of the atherosclerotic lesions. However, especially in advanced atherosclerotic lesions, lymphocytes (both T and B lymphocyte subsets) and plasma cells can be observed in the adventitial region, and occasionally form tertiary lymphoid structures with germinal centers [44,45]. Such adventitial lymphocytic infiltrates are considered to play a role in atherosclerotic lesion formation [46]. Although information is limited, we might question whether IgG4-related perivascular inflammation has any role in the development of coronary atherogenesis.

In some previous reports describing cases of IgG4-related coronary periarthritis, stenosis was not entirely present or was only mild at the site of the coronary artery surrounded by the severe periarterial soft tissue cuffs [26,27,30,38], suggesting that the severity of IgG4-related periarterial inflammation may not necessarily parallel coronary artery luminal narrowing irrespective of the presence of prominent adventitial immuno-inflammatory cell infiltration. On the other hand, physiologically significant stenosis was noted at the coronary artery surrounded by the IgG4-related pseudotumor in Tanigawa et al.'s patient [31].

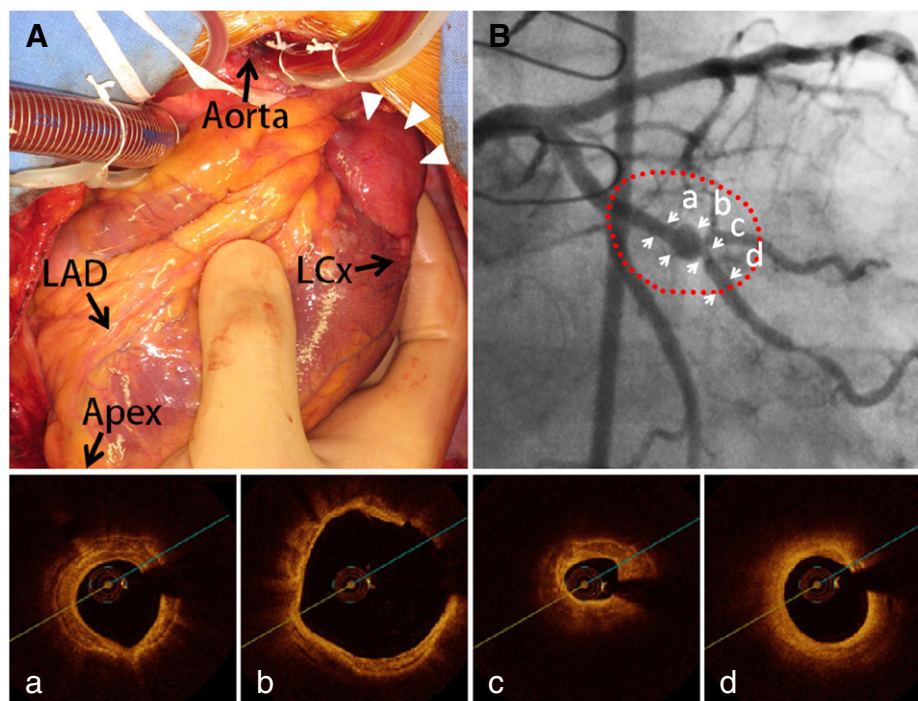


Fig. 1. Coronary artery pseudotumor. Upper panel, A. Picture at the time of surgery. Soft mass tissue surrounded the left circumflex artery (arrowheads). Upper panel, B. Invasive coronary angiography. Small aneurysmal region (b) and stenosis (c) can be observed. The broken line indicates the approximate area surrounded by the pseudotumor. Lower panels. Optical coherence tomography (OCT) images. a–d correspond to the levels indicated in B. Ring-like calcification can be observed at the site of aneurysmal dilatation (b). In addition to calcification of the coronary artery wall, intimal thickening is observed in the stenotic site (c). LAD, left anterior descending artery; LCx, left circumflex artery. Reproduced from [31] and [47] with modifications.

Tanigawa et al. performed intracoronary optical coherence tomography that showed neointimal formation and wall calcification (Fig. 1), resembling findings in Takayasu's arteritis, at the coronary artery encased by the inflammatory soft mass [47]. In addition, Sakamoto et al. examined the serum IgG4 levels in patients undergoing invasive coronary angiography. In their study population, no patient had apparent perivascular coronary inflammation [48]; however, serum IgG4 levels were higher in patients with significant coronary artery stenosis than those without (Fig. 4). They reported that, in a multivariate model, patients in the highest IgG4 quartile ($\text{IgG4} > 57.7 \text{ pg/mL}$) were more likely to have coronary artery disease than those in the lowest IgG4 quartile ($\text{IgG4} < 17.8 \text{ pg/mL}$) with an odds ratio of 3.75 (95% confidence interval 1.64–8.57). They also demonstrated that the relationship observed was not attributed to the increased prevalence of abdominal aortic aneurysm in patients with coronary artery disease [49]. These findings support the possibility that IgG4-related inflammatory reactions may have a role in the development of coronary atherosclerosis.

3. Associated conditions

Several reported cases of IgG4-related coronary periarthritis/pseudotumor had accompanying abnormalities that were diagnosed or suggestive of IgG4-related disease in other organs, including the aorta [26], pancreas [37], kidney [50], and parotid glands [27]. These findings are consistent with the notion that IgG4-related coronary periarthritis is one of the features of systemic IgG4-RD.

Maturen et al. recently reported two cases in which retroperitoneal fibrosis and coronary and aortic periarthritis were demonstrated by computed tomography (CT) [51]. Although neither measurement of serum IgG4 levels nor histological assessment of the thickened tissue was performed for either of these cases, it is possible both patients may have had IgG4-related systemic inflammation. Notably, in these cases, significant coronary artery stenosis that potentially induces myocardial ischemia-mediated symptoms was absent; thus, soft tissue encasing the coronary artery may have been overlooked if, instead of CT imaging, invasive coronary angiography was performed.

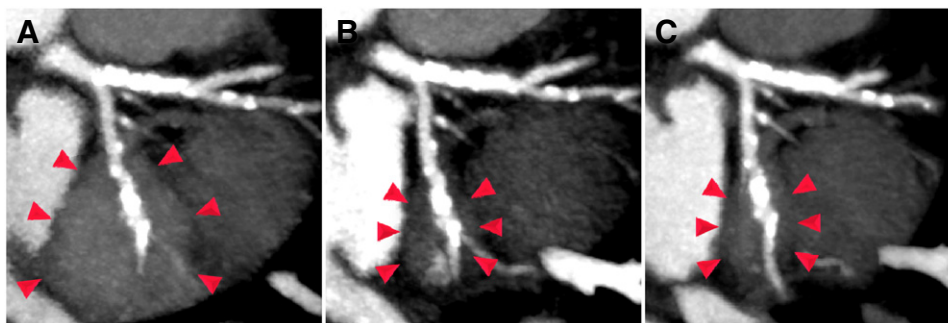


Fig. 2. Temporal changes in the size of the coronary pseudotumor (arrowheads) after bypass surgery. Size of the perivascular pseudotumor surrounding the left circumflex artery before coronary bypass surgery (A), and 230 days (B) and 409 days (C) post operation. Reproduced from [32] with modifications.

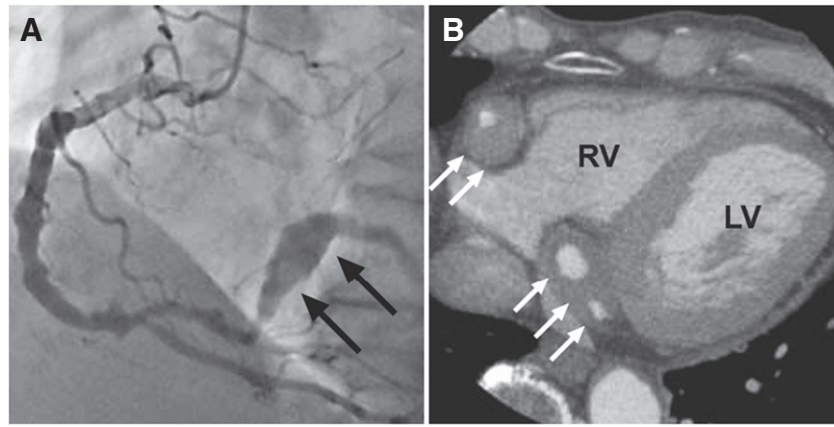


Fig. 3. Invasive coronary angiography and cardiac computed tomography (CT). A. Invasive coronary angiography shows generally ectatic right coronary artery with aneurysmal dilatation at the distal segment (arrows). B. Cardiac CT clearly demonstrates focal tumorous lesions surrounding the right coronary artery (arrows). RV, right ventricle; LV, left ventricle. Reproduced from [27].

4. Questions remaining to be answered

Because IgG4-RD is a new clinical entity, there are literally lots of unanswered questions. First, does IgG4 play a causal or protective role in the development of coronary periarthritis? It is known that IgG4 is unable to bind C1q complement and cannot activate the classic complement pathway [52]. It is even not certain IgG4-RD is an *autoimmune* disorder. Second, what is the prevalence of IgG4-related coronary periarthritis? As discussed above, coronary artery stenosis may not exist even when histologically proven IgG4-related coronary periarthritis/pseudotumor is present. Therefore, such perivascular abnormalities might have been overlooked in the era of invasive coronary angiography. More instances of IgG4-related coronary periarthritis may be identified by increased use of imaging modalities that can recognize periarthritic morphologies, such as CT and MRI. Third, what is the prognosis? Whether subjects who have IgG4-related pericardial inflammation are at higher risk for coronary artery disease and other cardiac events is not known. Considering the increasing usage of chest CT imaging as a screening tool, this point should be addressed in future studies. Fourth, what are the therapeutic strategies? As in the case of IAAA, corticosteroid therapy may improve the periarthritic thickening [30]; however, this therapy may not be able to inhibit coronary artery dilatation [27]. In addition, enhanced thrombogenicity may also be a concern for corticosteroid therapy

especially when there is a physiologically significant coronary stenosis. It was reported that following extracorporeal circulation, concentrations of serum IgG4 and size of IgG4-related coronary pseudotumor decreased without corticosteroid therapy [32]. Furthermore, the long-term efficacy of such therapy has not been proven. Considering that intra-coronary implantation of a drug-eluting stent (DES) may induce, albeit rarely, coronary aneurysms [53], it should also be questioned whether DES implantation would be an appropriate strategy for the treatment of coronary stenosis associated with IgG4-related periarthritis. Fifth, does IgG4-RD have associated co-morbidities? It has been reported that the possibility of concomitant malignancies may not be negligible in patients with IgG4-RD [54]; however, whether or not subjects with IgG4-related coronary periarthritic inflammation have a higher risk for malignant diseases is not known. Nevertheless, we should be aware that malignant lymphoma may be one such concomitantly presentable condition, the invasion of which might mimic the coronary artery pseudotumor [55]. To add to our perplexity, soluble interleukin-2 receptor, a marker of immune activation, may be elevated in both IgG4-RD and malignant lymphomas [37].

5. Conclusion

Recent studies have shown that coronary artery represents one of the targets of IgG4-RD, a newly emerging clinical entity. Although surgical or needle biopsy has been performed for diagnosis purposes and coronary artery periarthritis/pseudotumor has been treated by surgical removal or corticosteroid therapy in previously reported cases (Fig. 5), at present, we do not know what the optimal diagnostic and therapeutic strategies will be. Considering that IgG4-related, or non-related, coronary periarthritis may be more frequently discovered in parallel with the increasing use of CT and MRI, efforts should be taken to answer the questions raised above. In addition, physicians should be aware the possibility of the concomitant existence of malignancies in IgG4-RD, although whether or not patients with IgG4-related coronary periarthritis/pseudotumor have a higher risk for malignant disease remains to be elucidated.

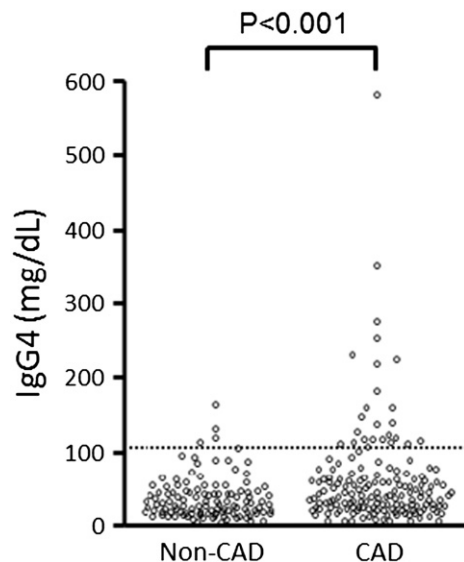


Fig. 4. Scattered plot of immunoglobulin G4 (IgG4) in patients with and without coronary artery disease (CAD). Reproduced from [48].

Abbreviations

IgG4	Immunoglobulin G4
CT	computed tomography
MR	magnetic resonance
PET	positron-emission tomography

Conflict of interest statement

The authors declare no competing financial interests.

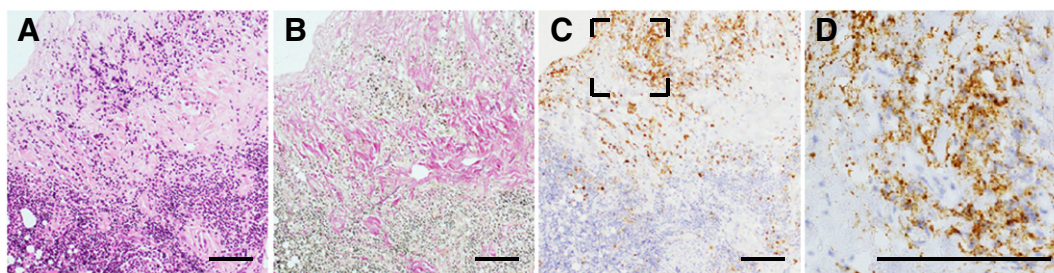


Fig. 5. Histological and immunohistochemical analysis of the IgG4-related coronary artery perivascular pseudotumor. A. Hematoxylin-eosin staining. Infiltration of numerous lymphocytes is observed. B. Elastica van Gieson staining. Abundant collagen fibers are shown. C and D. IgG4 staining. D is a high-power image of the bracketed area in C. Scale bars indicate 100 μ m. This case was reported in [31].

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