

A suspected case of coronary periarteritis due to IgG4-related disease as a cause of ischemic heart disease

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Abstract IgG4-related disease (IgG4-RD) is a systemic inflammatory disease characterized by marked infiltration of IgG4-positive (+) plasma cells into affected organs, but the concept of this disease has only recently been established. Coronary vasculitis is a rare disease that can cause sudden death, and it has recently been reported that IgG4-RD may be associated with vasculitis, including periarteritis and coronary disease. In this paper we report an autopsy case of sudden death of a man in his thirties, in which coronary periarteritis with features of IgG4-related periarteritis was detected. IgG4-RD was suspected from the presence of the following histopathological features: (1) markedly thickened adventitia and marked infiltration of the adventitia and periarterial fat by lymphocytes and plasma cells; and (2) infiltration of IgG4-positive plasma cells (ratio of IgG4+ cells to IgG4+ cells of >40 %, 50 IgG4+ plasma cells per high-power field) on immunostaining. The etiology and pathophysiology of IgG4-RD and IgG4-related periarteritis are still unclear, and further investigation of these conditions and their association with coronary lesions is needed. Careful consideration should be given to the possible presence of IgG4-RD when forensic pathologists encounter cases of sudden death accompanied by coronary periarteritis.

Keywords IgG4-related disease · Coronary vasculitis · Sudden death · Postmortem angiography · Periarteritis

Introduction

Coronary vasculitis is a rare disease that can cause sudden death [1]. It has recently been pointed out that IgG4-related disease (IgG4-RD), a systemic chronic inflammatory disease characterized by elevated serum IgG4 levels and marked infiltration of IgG4-positive plasma cells into affected organs [2], may be associated with vasculitis, including periarteritis and coronary disease [1, 3, 4]. Among the handful of clinical case reports on IgG4-related periarteritis to date [5–11], only one fatal case has been reported [12]. In this paper we report an autopsy case of sudden death of a man in his thirties, in which coronary periarteritis with features of IgG4-related periarteritis was detected. We describe the features of the disease and present diagnostic images acquired by post-mortem computed tomography with coronary angiography (PMCTA).

Case report

A 38-year-old man (height 178 cm, weight 89 kg) was found lying in an amusement arcade. He had experienced cardiopulmonary arrest and was confirmed dead at the hospital. A forensic autopsy was requested because the death had not been witnessed, and the cause was therefore unclear. In life, he had not complained of any symptoms and although hyperlipidemia had been pointed out at a routine health examination, he had no remarkable medical history. He smoked 20 cigarettes a day.

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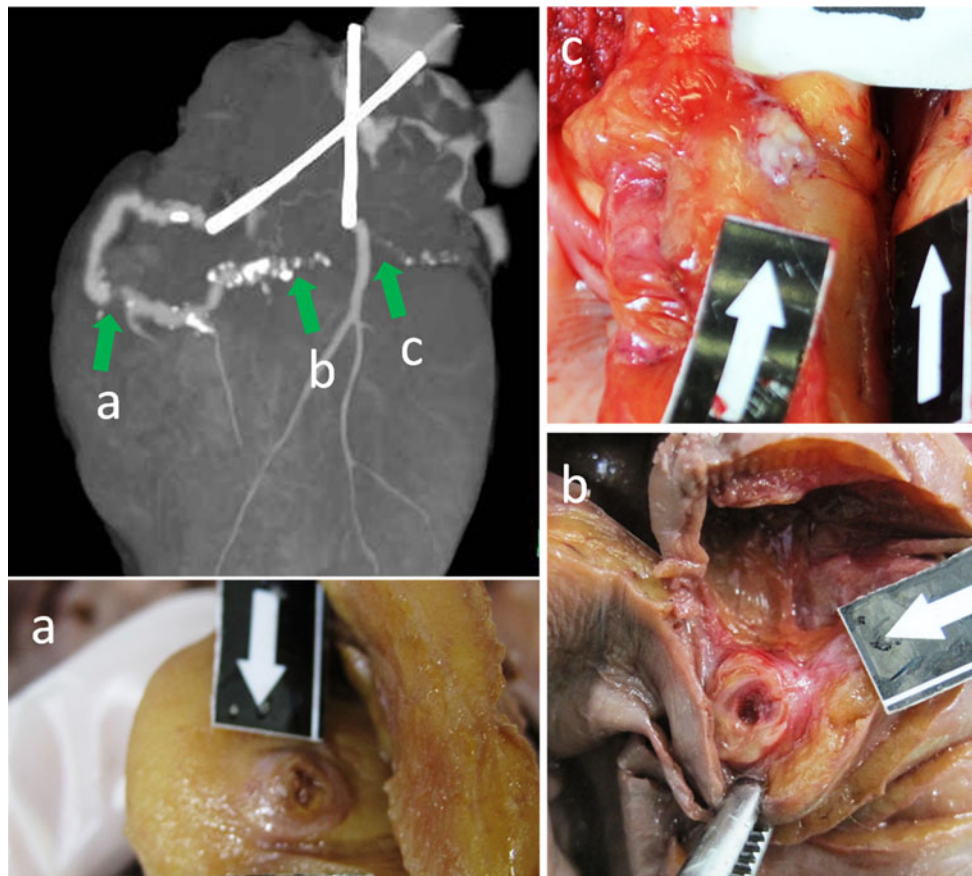


Fig. 1 Coronary angiography image showing a filling defect in the middle portion of the right coronary artery (RCA) (arrow *a*) and disruption of enhancement in the distal portion of the RCA and the origin of the left circumflex artery (arrows *b*, *c*). These findings

suggest a severely stenotic and occluded lesion, respectively. Autopsy revealed severe stenosis and occlusion due to atherosclerosis or thrombus at the same sites indicated on coronary angiography (**a–c**). The adventitia was markedly thickened at these lesions

Postmortem computed tomography findings

At our institute, postmortem computed tomography is routinely performed immediately before autopsy, using a 16-row multi-detector CT scanner (ECLIOS, Hitachi Medical Systems, Tokyo, Japan). The major findings in the present case were as follows: calcification of the coronary artery suggesting the development of atherosclerosis, and diffuse increased density of the bilateral lung resembling pulmonary edema.

Postmortem coronary angiography findings

To complement the diagnosis at autopsy, we also performed isolated heart PMCTA using a previously reported technique [13]. A detailed review was performed using image analysis software (SYNAPSE VINCENT 3D, Fujifilm Medical, Tokyo, Japan) after autopsy. Findings were a filling defect in the middle portion of the right coronary artery (RCA) (Fig. 1, arrow *a*) and disruption of enhancement in the distal portion (Fig. 1, arrow *b*), suggesting a

severely stenotic lesion and an occluded lesion, respectively. Disruption of enhancement was also detected at the origin of the left circumflex artery (LCX), suggesting an occluded lesion (Fig. 1, arrow *c*). The lumen where the RCA showed enhancement was diffusely irregular and the entire vessel wall showed thickening (Fig. 2). No stenotic lesion was detected in the left anterior descending artery (LAD) and lumen enhancement was smooth.

Autopsy findings

The heart weight was 500 g. In the coronary artery, severe stenosis and occlusion due to atherosclerosis and thrombus were detected in the middle and distal portions of the RCA, respectively, as indicated on angiography. The entire vascular wall of the RCA was thickened, and the degree of thickening was particularly severe at these lesions. In the LAD, mild intimal thickening due to atherosclerosis and no significant stenotic lesion were confirmed. The cut surface of the myocardium showed an area of white discoloration suggesting a fibrotic lesion in the posterior wall.

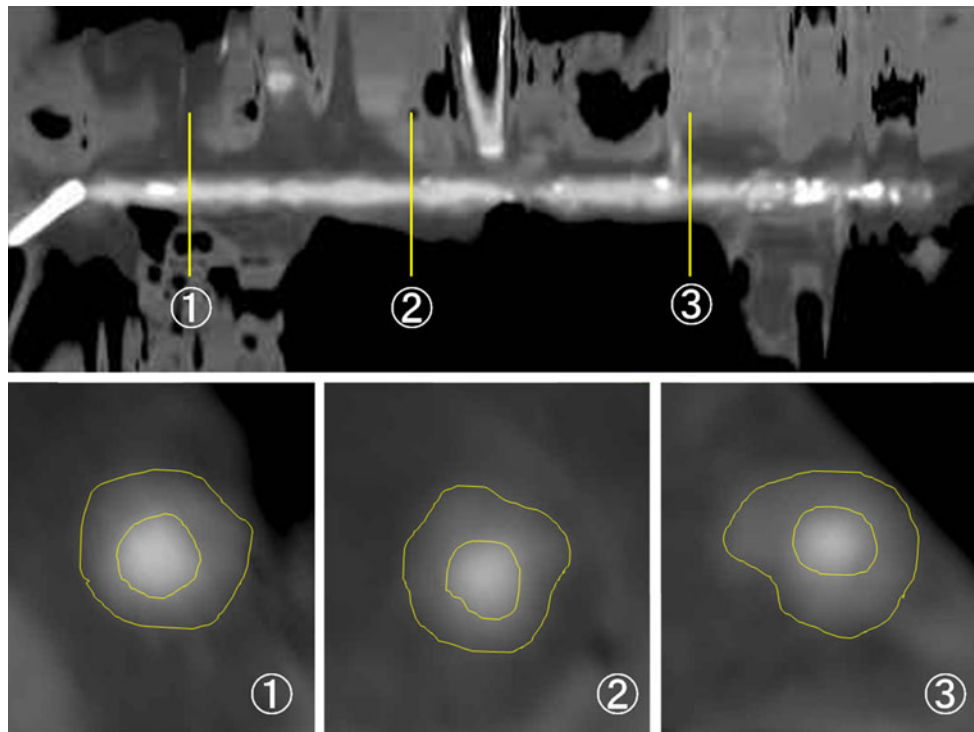


Fig. 2 Enhancement of the RCA shown on straight and curved planar reconstruction imaging. The lumen was diffusely irregular, and the entire vascular wall was thickened in parts other than the sites of

severe stenosis and occlusion [1–3]. The computed tomography value of the thickened vascular wall parts is 50–100 HU

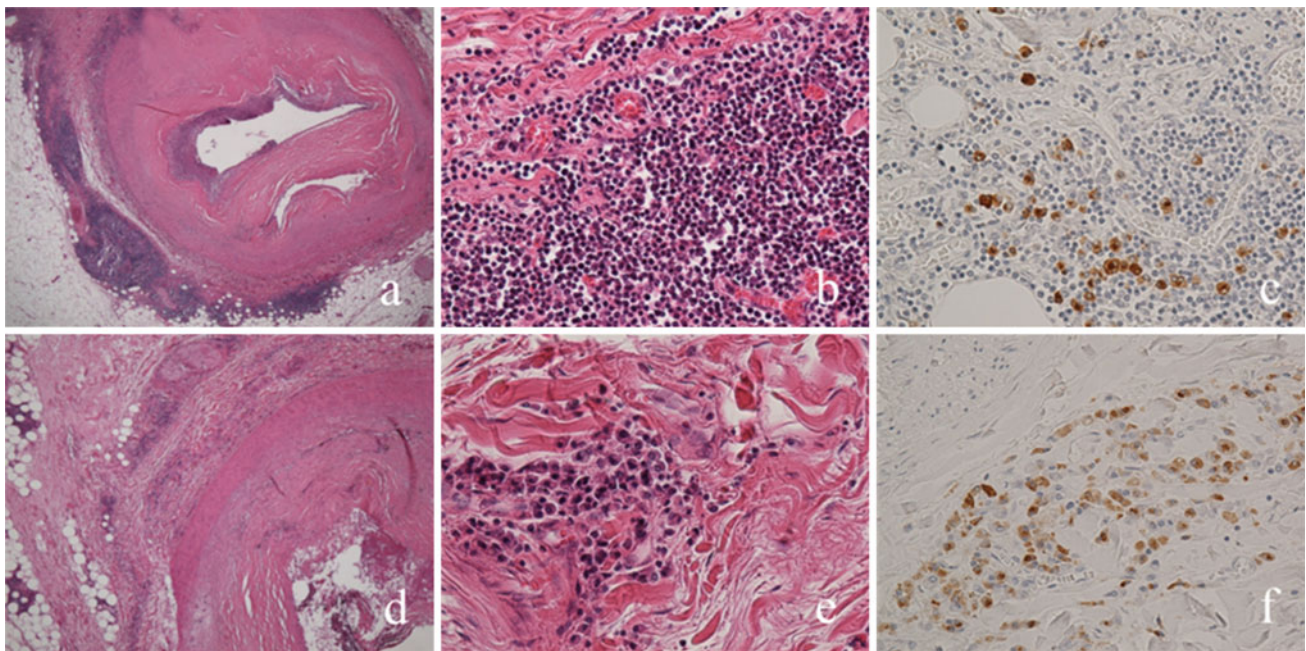


Fig. 3 Severe stenosis lesion in the middle portion of the RCA (**a** hematoxylin and eosin (H&E) $\times 40$; **b** H&E $\times 400$; **c** IgG4 immunostaining $\times 400$) and the occluded lesion in the distal portion of the RCA (**d** H&E $\times 40$; **e** H&E $\times 400$; **f** IgG4 immunostaining $\times 400$). At these locations, atherosclerotic lesions with severe calcification and hyaline fibrosis of the intima are evident, and inflammatory cells are follicularly distributed and markedly infiltrated into the adventitia and

the periarterial fat (**a**, **d**). Inflammatory cells are mainly lymphocytes and plasma cells (**b**, **e**). In the lumen of the middle portion, a layer of aggregated inflammatory cells can be seen under the endothelial cells (**a**). In the lumen of the distal portion, a relatively recently formed fibrin thrombus is apparent (**d**). IgG4 immunostaining revealed >50 IgG4+ plasma cells per high-power field in both lesions (**c**, **f**)

Histopathological findings

Atherosclerotic lesions with severe calcification and hyaline fibrosis of the intima were confirmed along the entire LCX and RCA. In these lesions, lymphocytes and plasma cells were follicularly distributed and markedly infiltrated the adventitia and periarterial fat (Fig. 3a, b, d, e). On the lumen side of the severely stenotic lesion in the middle portion of the RCA, a layer of aggregated inflammatory cells had formed under the endothelial cells (Fig. 3a). In the lumen of the occluded lesion in the distal portion of the RCA, a relatively recent fibrin thrombus had formed (Fig. 3d). No necrotic lesions were present in the vascular wall. In the severely stenotic and occluded lesions, IgG and IgG4 immunostaining showed >50 IgG4+ plasma cells per high power field (HPF) and a ratio of IgG4+ cells to IgG4+ cells of >40 % (Fig. 3c, f). In the LAD, mild intimal thickening due to atherosclerosis was detected, but no infiltration of lymphocytes or plasma cells into the adventitia was observed. In the posterior wall of the myocardium, marbling fibrotic lesions were detected.

Biochemical examination of blood findings

C-reactive protein was 0.3 mg/dl, IgG was 1,563 mg/dl (reference value: 870–1,700 mg/dl), and IgG4 was 109 mg/dl. Serum IgG4 was lower than the cutoff value (134 mg/dl). Rheumatoid factor, various antinuclear antibodies, and antineutrophilic cytoplasmic antibody (ANCA) were negative.

There were no obvious lesions suspected to be fatal macroscopically, histopathologically, or radiographically in other organs, so cause of death was determined to be ischemic heart disease due to coronary artery lesions.

Discussion

The notable differential diagnoses of coronary vasculitis contributing to sudden cardiac death are Takayasu's arteritis (TA), Kawasaki disease (KD), polyarteritis nodosa (PN), ANCA-associated vasculitis, collagen disease (e.g., systemic lupus erythematosus and rheumatoid arthritis), and infection [1]. In the present case, necrotizing arteritis such as PN seemed unlikely because no fibrinoid necrotic lesions were detected in the vasculature. There were also no typical histopathological features of KD, namely, infiltrative inflammation at all layers from the intima to the adventitia. Additionally, the various antibody tests were negative, and there were no symptoms suggestive of ANCA-associated vasculitis or collagen disease, and there seemed to be a general lack of findings of an infection with the potential to cause arteritis. Furthermore, although TA was not completely ruled out from the general

Table 1 Comprehensive clinical diagnosis (CCD) criteria for IgG4-RD, as appears in Umehara et al. [13]

| |
|---|
| Clinical examination shows characteristic diffuse/localized swelling or masses in single or multiple organs |
| Hematological examination shows elevated serum IgG4 concentration (≥ 135 mg/dl) |
| Histopathological examination shows: |
| Marked lymphocyte and plasmacyte infiltration and fibrosis |
| Infiltration of IgG4+ plasma cells: ratio of IgG4+ cells to IgG4+ cells of >40 % and >10 IgG4+ plasma cells per high-power field |
| Definite: 1 + 2 + 3 |
| Probable: 1 + 3 |
| Possible: 1 + 2 |
| However, it is important to differentiate IgG4-RD from malignant tumors specific to organs (e.g., cancer and lymphoma) and from similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg-Strauss syndrome) by additional histopathological examination |
| Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD |

histopathological features, immunostaining revealed that the present case had characteristics that were more similar to IgG4-related coronary periarteritis than to TA.

IgG4-RD is a systemic inflammatory disease characterized by marked infiltration of IgG4-positive plasma cells into various organs, such as the pancreas (autoimmune pancreatitis), lacrimal gland, submandibular gland (Mikulicz's disease), bile duct, kidney, aorta, and retroperitoneum, and the concept of IgG4-RD has only recently been established [2]. We conducted autopsy in this case without IgG4-RD in mind because this was a case of sudden death and there was limited information available on the clinical course. In addition, we could not collect specimens from the lacrimal gland or submandibular gland, although the sampling of various organs is important in autopsy. However, no marked lesions were observed macroscopically, histologically, or radiographically in the main organs, except in the coronary artery.

The histopathological features detected in the coronary artery were as follows: (1) marked thickening of the adventitia and marked infiltration of the adventitia and periarterial fat by lymphocytes and plasma cells (coronary periarteritis); and (2) infiltration of IgG4+ plasma cells (ratio of IgG4+ cells to IgG4+ cells >40 %, 50 IgG4+ plasma cells/HPF) on immunostaining resembling the features of previously reported IgG4 coronary periarteritis and satisfying the histological diagnostic criterion of "probable histological features of an aortic lesion" that recently gained consensus from IgG4-RD experts at an international symposium [14]. Thus, the findings in the present case were suggestive of IgG4-related coronary

periarthritis. However, the presence of a coronary lesion is not included in this criterion because IgG4-related coronary periarthritis is a particularly new concept in IgG4-RD and there has been no discussion yet on whether to adopt this aortic lesion criterion for diagnosis of the coronary artery. Using comprehensive diagnostic criteria that have been proposed by research groups organized by Japan's Ministry of Health, Labor, and Welfare (Table 1) [15], we could not reach a definite diagnosis in the present case because the serum IgG4 concentration was not elevated above the cutoff value of 135 mg/dl, and storiform fibrosis, which is a specific finding of IgG4-RD, was not detected. Nevertheless, the present case has features distinctly resembling IgG4-RD and cannot be classified as any of the previously described types of coronary vasculitis.

Although histopathological investigation is essential for the diagnosis of IgG4-RD, it cannot always be performed if the sampling organ is difficult to access for biopsy, such as is the case with the coronary artery. Thus, non-invasive imaging tests should be used for diagnosis, and consequently physicians should know its diagnostic imaging features [4, 11]. We routinely perform PMCTA for suspected cases of ischemic heart disease, and this modality provided valuable imaging features of IgG4-related coronary periarthritis in the present case. Previously reported imaging findings of IgG4-related coronary periarthritis include a large pseudo-tumor [5–7, 9], a coronary aneurysm [6, 8, 10, 12], and a low-density area around the artery on CT coronary angiography (CTCA) (pigs-in-a blanket) [11]. The present case showed no aneurysm or large pseudo-tumor but had a thickened vascular wall with slight enhancement (25–50 HU on non-enhanced CT images and 50–100 HU on enhanced images) extending into the entire right coronary artery close to the pigs-in-a blanket. Diffuse lumen irregularity was also confirmed. If similar findings are confirmed on vital CTCA, careful observation is needed by considering the possibility of IgG4-related coronary periarthritis and by conducting additional investigation.

The most important concern is whether or not IgG4-related coronary periarthritis should be accepted as a primary cause of death, even if this was actually true in the present case. In other words, the present findings reflect one of the following scenarios: either that (1) the IgG4-related immune inflammatory response itself was the cause of the coronary artery lesions, or (2) was one of the factors that triggered lesion development, or that (3) IgG4-positive cells infiltrated into the adventitia during the terminal stage of atherosclerosis. Scenarios (1) and (2) are possible because the immunological response of regulatory T cells is activated in IgG4-RD, and TGF β —a cytokine produced by regulatory T cells may be related to the formation of the fibrotic and arterial lesions [2, 17]. Serum IgG4 levels have been reported to be higher in patients with significant coronary artery stenosis than in those without [18]. However,

the exact mechanism of lesion formation in IgG4-RD has still to be elucidated, and there is little consensus on whether or not IgG4-RD is related to the formation of coronary lesions [4]. Because hyperlipidemia was found on autopsy in the present case, and because the individual had been a heavy smoker, the coronary lesions may have developed due to atherosclerosis in the usual manner. Atherosclerosis was extremely severe even though the subject was in his thirties, and in addition to a wide variety of lesions, significant infiltration of IgG4+ plasma cells was observed in the RCA, but not in the LAD which showed only mild intimal thickening. Therefore, as in (3), it is possible that the IgG4-related immune inflammatory response occurs at a certain stage of coronary artery disease and contributes to the development of coronary lesion.

Although steroids are typically the first line of therapy for IgG4-RD [2], both cases of effective [9] and non-effective treatment for coronary lesions have been reported, and decreases in serum IgG4 levels and in pseudo-tumor size have been confirmed without the administration of steroids [16]. In addition, steroids should be prescribed sparingly because they tend to promote thrombosis and may diminish coronary circulation [4]. To decide on the appropriate therapeutic strategy, further investigation of the etiology and pathophysiology of IgG4-RD and its association with coronary lesions is needed. Careful consideration should be given to the possible presence of IgG4-RD when forensic pathologists encounter cases of sudden death accompanied by coronary periarthritis.

Key points

1. IgG4-related periarthritis, a new concept of disease, may cause coronary lesions and lead to sudden cardiac death.
2. CTCA imaging findings are thickened vascular walls with slight enhancement and diffuse lumen irregularity.
3. The etiology and pathophysiology of IgG4-related periarthritis, and its association with coronary lesions, are still unclear. Further investigations are needed, and forensic pathologists should consider the possibility of this disease when coronary periarthritis is detected in cases of sudden death.

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