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CASE BASED REVIEW

Myocardial ischemia as presenting manifestation of IgG4-related disease: a case-based review

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Abstract Coronary involvement in IgG4-related disease (IgG4-RD) has been scarcely reported, and myocardial ischemia as its presenting feature is even rarer. Here, we describe an additional case with novel and relevant observations. The patient was a previously healthy, middle-aged woman who presented to the clinic with new-onset typical angina. One tumefactive lesion encasing the left anterior descending artery was found during her workup. The most common underlying malignancies with secondary cardiac involvement were rationally ruled out. Symptoms persisted despite medical treatment, and she was therefore referred to surgery. Tumor excision was successfully performed, and she received coronary bypass grafting. IgG4-related coronary arteritis with pseudotumor formation was subsequently diagnosed following the comprehensive diagnostic criteria. This condition was clinically classified as active and circulating plasmablasts were found to be increased (5480/mL), even when these were determined 38 days after surgery. A PET/CT revealed an additional hypermetabolic lymph node. She was therefore treated with rituximab as induction therapy (two 1000 mg doses, administered 15 days apart). Three months later, her disease remained clinically inactive. Circulating plasmablasts were repeated and these had dropped to 0/mL. We thereafter review the current and pertinent literature on the topic, emphasizing the previous cases with similar presenting features ($n = 7$). We lastly suggest that IgG4-RD should be part of the differential diagnosis of any patient with tumefactive lesions surrounding the coronary arteries, since it can initially presented as sudden cardiac death.

Keywords Coronary arteritis · Coronary artery bypass · IgG4-related disease · Plasmablast · Rituximab

Introduction

IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition that can affect almost any organ or system in the body and often leads to tumefactive lesions. Most patients have

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multiorgan involvement; others show involvement of a single organ nevertheless [1–3]. Coronary involvement has been scarcely reported in the literature [2], and myocardial ischemia as its presenting feature is even rarer [1, 4]. In the latter cases, lymphoplasmacytic arteritis is not the typical histopathological picture [5, 6]. Circulating plasmablasts have been recently proposed as a biomarker for diagnosis and follow-up of IgG4-RD, and may be particularly useful in patients with normal serum IgG4 levels [7]. B cell depletion is an effective therapy for IgG4-RD and may be appropriate as first-line treatment in patients with contraindications to corticosteroids [8–11]. Here, we describe the case of a previously healthy, middle-aged woman who presented to the clinic with myocardial ischemia secondary to IgG4-related coronary arteritis with pseudotumor formation, and who was effectively treated with tumor resection and rituximab. We then review the relevant and current literature on the topic, emphasizing the previous cases with similar presenting features.

Case presentation

A previously healthy 44-year-old woman presented to the clinic with a 1-week history of typical angina. She denied any family history of coronary heart disease as well as tobacco or illicit drug use. While she had not been previously diagnosed with hypertension, she was found to be hypertensive with blood pressure of 150/105 mmHg. She underwent exercise treadmill testing based on the Bruce protocol and the latter was considered positive for ischemia. Coronary computed tomography angiography (CCTA) was thus performed and showed a tumefactive lesion encasing the proximal segment of the left anterior descending coronary (LAD) artery (Fig. 1a). The most common underlying malignancies with secondary cardiac involvement were rationally ruled out. Symptoms persisted despite medical treatment, and she was therefore referred to surgery (Fig. 1b). The tumor was entirely resected, and she received double coronary bypass grafting (left internal mammary artery to LAD artery and saphenous vein graft to obtuse marginal artery). Intraoperative histologic examination revealed plasma cell arteritis.

She was then transferred to the intensive care unit (ICU), where, on her third postoperative day, she suffered a wake-up ischemic stroke in the right middle cerebral artery territory. No hemorrhagic changes were detected on T2*-weighted gradient-echo imaging. Intravenous thrombolysis was not administered because of infract size and major surgery within the previous days. As this event was classified as malignant, a decompressive hemicraniectomy was successfully performed. Transesophageal echocardiography revealed normal atrial dimensions with left appendage thrombus, moderate mitral regurgitation, and normal left ventricle dimensions with hypokinetic basal anterior, mid-anteroseptal, basal

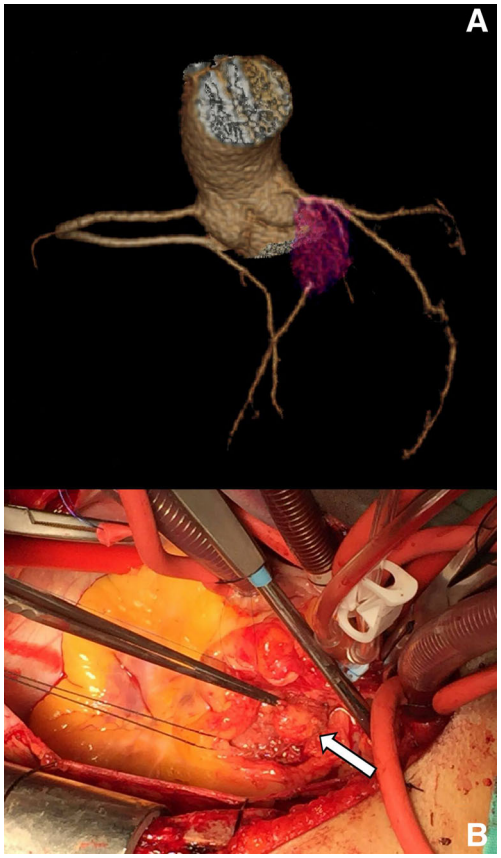

Fig. 1 **a** Coronary computed tomography angiography (volume-rendering technique). The pseudotumor (*in purple*) is encasing the proximal segment of the left anterior descending coronary artery. Image courtesy of Dr. Karla Nuñez-Barragan and Prof. Guillermo Elizondo-Riojas, University Center for Diagnostic Imaging, University Hospital, UANL. **b** Intraoperative view before tumor excision. The *white arrow* denotes the location of the pseudotumor

anteroseptal, and mid-anterior segments. The left ventricular ejection fraction was estimated to be more than 50 %. All other parameters were within the normal limits. Her blood pressure was under control, and she was started on unfractionated heparin 48 h after surgery. On the next day, she had neurological deterioration and a CT scan showed a type 2 parenchymal hematoma; aPTT was below the therapeutic range at that time. Therefore, the patient was taken once again to the operating room, and the clot was successfully evacuated. Her neurological status began to improve thereafter, and she was later extubated uneventfully. One episode of paroxysmal atrial fibrillation was detected during her stay in the ICU. In the course of this very stay, she also developed *Pseudomonas aeruginosa* ventilator-associated pneumonia, which was effectively treated with ceftazidime/ciprofloxacin. After 18 days in the ICU, she was transferred to the general ward.

A 1.5 × 1.2 × 1-cm piece of tissue was received for histopathological examination. Macroscopically, this piece was light brown, with irregular borders, in one of which an arterial lumen was identified. Microscopic evaluation of excised

tissue revealed an intense, lymphoplasmacytic infiltrate in all layers of the arterial wall (Fig. 2a), which induced an intense, subintimal fibroblastic proliferation with complete luminal obstruction. Rupture of the internal elastic lamina and thickening of the media and adventitia were also seen. Phlebitis and storiform fibrosis were alike observed (Fig. 2b, c). ALK was not detected. Immunohistochemical staining revealed >20 IgG4 + plasma cells per high-power field (hpf) and an IgG4+/IgG+ ratio of 61 % (Fig. 2d, e). In the setting of this histologic constellation, IgG4-RD was suspected.

On further questioning, she denied unintentional weight loss, rash, red eye, oral, nasal or genital ulceration, or any familiar or personal history of atopic diseases. Her routine preoperative testing was within the normal range: hemoglobin of 13.3 g/dL; absolute eosinophil count, 180/μl; platelet count, 150,000/μL; and albumin-to-globulin ratio, 1.5. Additional tests were consequently ordered as a part of our diagnostic work-up, whose results were as follows: normal total IgG and IgG4 levels (1210 and 99.7 mg/dL, respectively), elevated total plasmablast count (TPC, 5480/mL), elevated erythrocyte sedimentation rate (49 mm/h), normal C-reactive protein levels, positive antinuclear antibodies (1:160, homogenous pattern), normocomplementemia, and negative VDRL test. Rheumatoid factor (RF) and antineutrophil cytoplasmic antibodies (ANCAs) were also negative.

Based on previous findings, a probable case of IgG4-RD was diagnosed according to the comprehensive diagnostic criteria [3]. Her disease was classified as active using the Responder Index [8, 12]. Forty-five days after tumor excision, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) was performed to evaluate the actual extent of disease. In general, thoracic and cardiac findings were interpreted as postoperative changes. Residual tumor could not be excluded, since a soft tissue density ovoid mass (1.6 × 1 cm) was detected at the same location where the original pseudotumor was situated. An additional hypermetabolic right level IIA lymph node was found ($SUV_{max} = 4.7$). This node had normal morphology. On a follow-up CCTA, both grafts were patent and this heterogeneous, soft tissue density mass was interpreted as postoperative changes. She was treated with two 1000 mg doses of rituximab, administered 15 days apart. Anticoagulant therapy was resumed 38 days after the incident hemorrhagic

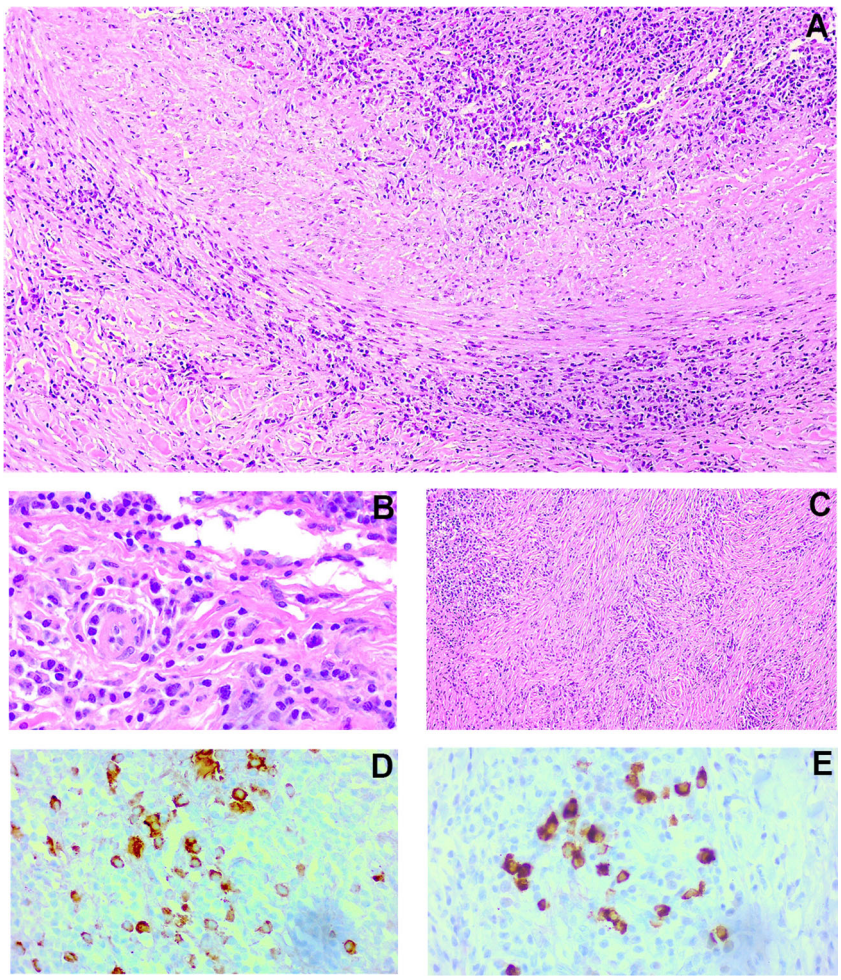

Fig. 2 **a** Microscopic view of the left anterior descending artery reveals a dense lymphoplasmacytic infiltrate in the tunica intima and media, which also obstructs the lumen (hematoxylin and eosin staining, × 5). **b** A higher-power view of obliterative phlebitis. Intramural plasma cells infiltration and obliteration of the lumen is evident (hematoxylin and eosin staining, × 40). **c** Storiform pattern fibrosis (hematoxylin and eosin staining, × 10). **d**, **e** Strong immunoreaction for IgG4 + plasma cells. In these frames, >20 IgG4 + plasma cells/high power field (HPF) and an IgG4+/IgG+ plasma cells ratio of 57 % are shown (×40)

transformation. Apixaban (2.5 mg twice daily) was chosen over vitamin K antagonists due to its safer profile. Follow-up transesophageal echocardiography was done after 22 days and showed complete thrombus resolution. At 3 months after rituximab administration, TPB was repeated and it had dropped to 0/mL. At present, the patient's hemiparesis improved (modified Rankin Scale of 4), she is afebrile and has no symptoms of either myocardial ischemia or anticoagulant-associated bleeding.

Discussion

Coronary artery involvement in IgG4-RD was first described in 2008 by Matsumoto et al., who demonstrated an elevated IgG4+/IgG+ ratio (59.2 %) in a tumefactive lesion surrounding the mid portion of the right coronary artery (RCA). According to the comprehensive diagnostic criteria, this patient can be now classified as a definite case of IgG4-RD [3, 13]. Involvement at this level has been rarely reported thenceforth [4]. Kusumoto et al. reviewed the literature on this topic up to 2011 and Guo et al. up to early 2013. They found only 10 cases of coronary involvement [4, 14], since then 13 additional cases have been reported (Table 1) [4, 5, 15–24]. The age of these cases ranged from 38 to 91 years with a mean of 67 years and all of them were male. Some reports were not included in the previous figures (neither in Table 1) due to the paucity of relevant information [25–27]. Lastly, inflammatory pseudotumors are now regarded as manifestations of IgG4-RD and, when they arise from the heart, only rarely involve the coronary arteries (7 cases in a recent, comprehensive review) [3, 28, 29].

Our patient's initial symptom was typical angina. Fujii et al. were probably the first who described a case of myocardial infarction (MI) as inaugural manifestation of IgG4-RD. This patient was an 83-year-old man with MI due to IgG4-related coronary periarteritis, in whom this involvement was further complicated with aneurysm formation. His serum IgG4 levels were elevated (2630 mg/dL), and he showed multiorgan involvement. Specimens for pathological examination were obtained by percutaneous renal biopsy. He was treated with percutaneous coronary intervention and corticosteroids, but died 3 months later from thoracic aortic aneurysm rupture [14, 30, 31]. In 2012, Tanigawa et al. described a similar case in the English language literature [32]. Myocardial ischemia as presenting feature of IgG4-RD has been reported a few times ever since (Table 2); more than a half of these diagnoses have been made postmortem [5, 17, 21, 24, 31]. All these four patients who suddenly died also had (at least) moderate-to-severe atherosclerosis. Of these, three had single organ involvement. Furthermore, in cardiac pseudotumors, an initial presentation of sudden death most often involves the coronary arteries [29]. Not all patients with

Table 1 Recent reports of IgG4-related coronary artery disease

Case	Authors	Country	Year	Gender	Age	Artery	Coronary lesion	Coronary histology	CVRF	Atherosclerosis	Organ involvement	IgG4 (mg/dL)	PET	Diagnosis	Treatment	Prognosis	Follow-up
1	Kan-o et al.	Japan	2013	M	68	RCA, LCA	A, S	NP	NR	NR	>2	1360	NP	Definite	Qx, CS	Improved	1 mo
2	Tong et al.	Singapore	2014	M	64	RCA, LCA	PT, E, S	NP	HTN, TU	NR	≤2	NR	Positive	Probable	CS, MMF	Improved	5 mo
3	Patel et al.	USA	2014	M	53	RCA, LCA	PT, S	LPA + SF + OP + IgG4	NR	Severe	>2	NP	NP	Probable	None	SCD	
4	Inokuchi et al.	Japan	2014	M	38	RCA, LCX	S	LPPA + IgG4	DL, TU	Severe	Single	109	NP	Probable	None	SCD	
5	Ebe et al.	Japan	2014	M	66	NR	NS	NP	NR	NR	>2	323	Positive	Possible	CS	Improved	7 mo
6	Tajima et al.	Japan	2014	M	68	NR	PT	LPPA + IgG4	NR	NR	>2	2390	Positive	Definite	CS	Died	6 mo
7	Bito et al.	Japan	2014	M	69	RCA, LCA	A	LPPA + IgG4	Negative	NR	≤2	161	NP	Definite	Qx, CS	NR	
8	Treacy et al.[a]	UK	2015	M	76	RCA	PT	LPPA + IgG4	HTN, AAR	Severe	Single	NP	NP	Probable	None	Died	
9				M	91	RCA	PT	LPPA + IgG4	Negative	Moderate-to-severe	Single	NP	NP	Probable	None	Died	
10	Kusunose et al.	Japan	2015	M	80	RCA, LCA	A, PT	NP	NR	NR	≤2	1210	Positive	Definite	CS	Improved	6 mo
11	Hamanaka et al.	Japan	2015	M	57	NR	PT	NP	NR	NR	Single	356	Positive	Definite	NR	NR	
12	Guo et al.	USA	2015	M	88	NR	Thickening	NP	HTN, TU	NR	NR	28	Positive	Probable	CS	Improved	4 mo
13	Benson et al.[a]	USA	2015	M	54	RCA, LCA	A, S	NR	NR	NR	>2	1980	Positive	Definite	Qx, CS, RTX	Improved	18 mo

A aneurysm, *AAR* aortic aneurysm repair, *CS* corticosteroids, *CVRF* cardiovascular risk factors, *DL* dyslipidemia, *E* ectasia, *HTN* hypertension, *LCA* left coronary artery, *LCX* left circumflex artery, *LPA* lymphoplasmacytic arteritis, *LPPA* lymphoplasmacytic periarteritis, *MMF* mycophenolate mofetil, *NP* not performed, *NR* not reported, *OP* obliterative phlebitis, *PET* Positron emission tomography, *PT* pseudotumor, *Qx* surgery, *RCA* right coronary artery, *RTX* rituximab, *S* stenosis, *SCD* sudden cardiac death, *SF* storiform fibrosis, *TU* tobacco use

[a] Personal communication

Table 2 Myocardial ischemia as presenting feature of IgG4-RD

Case	Authors	Country	Year	Gender	Age	Clinical presentation	CVRF	Atherosclerosis	Organ involvement	Diagnosis	IgG4 (mg/dL)	Treatment	Prognosis
1	Fujii et al. [a]	Japan	2010	M	83	MI	NR	NR	Multiple	Definite[b]	2630	CS	Died[c]
2	Tanigawa et al.	Japan	2012	M	66	MI	NR	NR	Single	Definite[b]	564	Qx	Relapse
3	Urabe et al. [a]	Japan	2012	M	84	MI	NR	NR	Multiple	Definite[b]	2630	CS	Died[c]
4	Patel et al.	USA	2014	M	53	MI	NR	Severe	Multiple	Probable	NP	None	Died
5	Inokuchi et al.	Japan	2014	M	38	MI	DL, TU	Severe	Single	Probable	109	None	Died
6	Treacy et al.	UK	2015	M	76	SCD	HTN, AAR	Severe	Single	Probable	NP	None	Died
7				M	91	SCD	Negative	Moderate-to-severe	Single	Probable	NP	None	Died
8	Benson et al.	USA	2015	M	54	MI	NR	NR	Multiple	Definite	1980	Qx, CS, RTX	Improved

AAR aortic aneurysm repair, *CS* corticosteroids, *CVRF* cardiovascular risk factors, *DL* dyslipidemia, *HTN* hypertension, *MI* myocardial infarction, *NP* not performed, *NR* not reported, *Qx* surgery, *RTX* rituximab, *SCD* sudden cardiac death, *TU* tobacco use

[a] These authors probably reported the same case

[b] IgG4 + plasma cells were not quantitatively assessed (or reported). See Discussion

[c] This patient died three months after presentation due to acute thoracic aortic rupture

IgG4-RD who have had myocardial ischemia or chest pain were included in Table 2 [33–36], but only those whose presenting manifestation was myocardial ischemia.

At present, there are no organ-specific criteria for diagnosing IgG4-related coronary artery disease [37], but a comprehensive set of criteria have been already proposed for the diagnosis of IgG4-RD [3]. These criteria were recently validated using a Japanese registry cohort. However, this registry cohort did not included patients with coronary involvement [38]. Histopathologic examination is central in the diagnosis of IgG4-RD [3, 39]. Nevertheless, it is often difficult to obtain antemortem tissue samples from some sites, such as the coronary arteries [3, 37]. Thus, when the clinician is faced with a patient with single-organ involvement (especially if it affects sites that are difficult to biopsy), the diagnosis becomes a special challenge. The latter is obvious in Table 1, where it is clear that only one patient with single-organ coronary involvement was diagnosed before dying. Obtaining an antemortem biopsy from these patients typically required a high-risk surgical procedure. Hamanaka et al. recently described that, in these cases, thoracoscopic biopsy is another possible approach [23].

Histopathological features are dependent on the affected organ [5]. The tunica adventitia is usually the primary site of arterial inflammation [6]. Intimal and medial involvement (a true vasculitis/arteritis) has been also described in the coronary arteries [5], but this is not the typical histopathological picture. In fact, lymphoplasmacytic coronary artery vasculitis as a cause of sudden cardiac death is fairly uncommon (0.2 % in a Londoner database) [40]. In the setting of this fibroinflammatory condition, IgG4 + plasma cells are generally present diffusely in most of the affected sites and focal aggregation is atypical [2, 39]. However, the distribution of these plasma cells may be patchy [39, 41]. In general, IgG4 + plasma cell infiltration in malignancies is also patchy, but in these cases, it is not associated with other histological hallmarks of IgG4-RD [39]. In our patient, while IgG4 + plasma cell distribution may be described as patchy, histopathological examination was not compatible with malignancy. As suggested above, the absolute number of IgG4 + plasma cells must be interpreted according to the affected organ [2, 39]. Due to its infrequency, a proposed cutoff value for coronary involvement was not included in the pathological consensus statement. As long as their distribution may be patchy, restricting our count just to areas of intense infiltrate (the so-called hot spots) might be more representative [39]. IgG4+/IgG+ ratio is more useful than the absolute count in diagnosing IgG4-RD, and a ratio of more than 40 % is mandatory to diagnose this condition. Nevertheless, on average, this ratio has not been precisely reported in the most recent cases of coronary involvement [4, 5, 15–24], except for Bito et al., who calculated an IgG4+/IgG+ ratio of 89 % [20]. Corradi et al. recently wondered if it is judicious to assume that cases slightly below the 40 % cutoff value can be classified as different conditions

[41]. Before the recognition of IgG4-RD as a separate and unifying clinical condition, several cases of atypical coronary artery disease were described. Many of these cases could be interpreted today as manifestations of IgG4-RD [28, 42]. Fibrosis is also needed for the diagnosis of IgG4-RD, and it can be found even in patients who recently started with their symptoms. Storiform or swirling fibrosis is characteristically associated with this disease. However, due to its patchy nature, sometimes this pattern is not detected. Fibrosis is likewise dependent on the affected organ [2, 3, 39], and Corradi et al. reported that purely storiform pattern is quite uncommon in coronary artery specimens. These authors also noted that obliterative phlebitis is not always detectable in vascular/perivascular involvement [41].

Elevated serum IgG4 levels (≥135 mg/dL) are also part of the comprehensive diagnostic criteria [3]. However, these levels may be normal in up to fifty percent of patients even in the presence of histological hallmarks [1, 26, 43]. In addition, still in the absence of corticosteroids, these levels drop after coronary bypass grafting. Tanigawa et al. reported that they dropped by nearly half 1 month after surgery [44]. This finding may account for the normal IgG4 levels in our patient, since these were determined 29 days after surgery. These levels returned to their preoperative value approximately one year after surgery [44]. Relapses may also occur in patients who have persistently normal IgG4 levels [2]. Given these limitations, TPC in peripheral blood have recently been proposed as a biomarker for diagnosis and monitoring of disease activity [2]. Immunophenotyping was consequently carried out in our facilities using flow cytometry, and CD19+CD20–CD27+CD38+ cells were defined as plasmablasts. TPC was found to be increased in our patient (5480/mL), even when these were determined 38 days after surgery. Among patients with IgG4-RD, TPC is significantly higher in those with >2 organs involved. Wallace et al. reported that a TPC of 2000/mL has a sensitivity of 87 % and a specificity of 91 % for the diagnosis of IgG4-RD. Following rituximab treatment, the mean percentage change in TPC between flare and remission was 66 %. Nevertheless, those with coronary involvement were not included in this study [7]. In the largest cohort to date, TPC was moderately correlated not only with serum IgG4 levels, but also with the Responder Index [8, 12, 26]. Among those with active disease, there was no difference in TPC according to sex. Patients with active disease and normal serum IgG4 levels had a median TPC equivalent to those with elevated IgG4 levels. One patient in this cohort had coronary involvement [26]. The role of CCTA in the setting of IgG4-RD is out of the scope of this mini-review and has been recently addressed elsewhere [45]. PET/CT has been previously used in cases with coronary involvement and may demonstrate hypermetabolic activity in perivascular soft tissue [4, 16, 24, 31]. This imaging modality can provide information about the actual extent of disease and also can demonstrate a more accessible site for biopsy [16]. Minor salivary gland biopsy may be diagnostic even in the absence of PET/CT findings [19]. While the utility of serial PET/CT has not been yet demonstrated [11], corticosteroids may decrease ^{18}F-FDG accumulation in coronary pseudotumors after 2 months of treatment [22].

Lymphoplasmacytic response to atheroma constitutes a major differential diagnostic consideration in those with suspected coronary artery vasculitis [40]. Atheromatous coronary arteries were not demonstrated in our patient. However, all those four patients who suddenly died had (at least) moderate-to-severe atherosclerosis (Table 2). Serum IgG4 levels may be increased in these patients with angiographically proven coronary atherosclerosis. While isolated coronary artery involvement is exceedingly rare in syphilis, this infection also needs to be excluded before diagnosing IgG4-related coronary artery disease [21]. Antinuclear antibodies may be present in up to 5 % of patients with IgG4-RD [1]. Nonetheless, systemic lupus erythematosus is classically associated with lymphoplasmacytic vasculitis, and therefore, it must be rationally ruled out [40]. Such conduct should be alike applied to rheumatoid arthritis, inasmuch as it is also associated with lymphoplasmacytic vasculitis and RF may be present in up to 20 % of those with IgG4-RD [1, 40]. Extranodal Rosai-Dorfman disease with coronary involvement probably does not belong to the spectrum of IgG4-RD, since IgG4 + plasma cells are not increased in this condition [32]. As in our case, prior to diagnosing IgG4-RD with coronary involvement, Takayasu arteritis, Kawasaki disease, polyarteritis nodosa, and ANCA-associated vasculitis must be also excluded on clinical and histopathological grounds [4, 17, 32, 40, 46]. Malignancy as a differential diagnosis was briefly addressed above.

Corticosteroids are the first-line treatment in IgG4-RD [1, 2], and also appear to be effective in patients with coronary pseudotumors [22]. However, we did not start our patient on corticosteroids due to the risk of increased thrombogenicity. A similar clinical situation has been previously described [44]. Even in the absence of corticosteroids, rituximab is an effective induction therapy for IgG4-RD. Therefore, it may be appropriate as first-line treatment in those with contraindications to corticosteroids [8–11]. Yamamoto et al. reported the effective use of lower doses [9, 10]. It is worth mentioning that patients with coronary involvement were not included in these studies [8]. Before our report, in these patients, rituximab has only been used in conjunction with corticosteroids [24]. In addition, Della-Torre et al. recently reported that rituximab also decreases the fibrotic process, characteristic of this disease, by attenuating the secretory phenotype of myofibroblasts [47]. The reduction of this fibrotic process is fundamental. The latter is especially true in the case of coronary involvement, since it can be fatal and initially presented as sudden cardiac death [5, 17, 21]. Regarding surgical revascularization, Tanigawa et al. reported vein graft failure approximately one year after surgery [48].

In summary, IgG4-RD should be part of the differential diagnosis of any patient with tumefactive lesions surrounding the coronary arteries, since it can be fatal. In addition, TPC may be useful for diagnosis and monitoring of this kind of patients, and PET/CT can demonstrate a more accessible site for biopsy. Lastly, rituximab may offer an effective induction therapy for these patients with IgG4-RD.

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Compliance with ethical standards

Disclosures None.

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