ESC European Society of Cardiology

European Heart Journal - Case Reports (2019) **3**, 1–5
doi:10.1093/ehjcr/ytz013

CASE REPORT
Coronary heart disease

Coronary artery disease concomitant with immunoglobulin G4-related disease: a case report and literature review

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Received 5 August 2018; accepted 26 January 2019; online publish-ahead-of-print 18 February 2019

Background Immunoglobulin G4-related disease (IgG4-RD) is an autoimmune condition associated with high serum IgG4 levels which was first reported as autoimmune pancreatitis in 2001. Since then, many additional organs, such as bile duct, salivary gland, retroperitoneal organs, and liver, have been reported with high serum IgG4 levels in cases of IgG4-RD. However, evidence of the relationship between IgG4-RD and coronary artery disease (CAD) has been scare. Here, we report a case of CAD concomitant with IgG4-RD.

Case summary A 74-year-old man was referred to our hospital with a chief complaint of chest pain and was admitted. The patient was found to have had a myocardial infarction with ST-segment elevation and underwent an emergent percutaneous coronary intervention. Owing to a rapidly increased blood glucose level, computed tomography was performed and showed autoimmune pancreatitis. An elevated serum level of IgG4 led to a diagnosis of IgG4-RD involving acute coronary syndrome (ACS).

Discussion Cardiac involvement in IgG4-RD has been reported; however, cases of ACS concomitant with IgG4-RD are rare. Our report suggests that CAD, specifically ACS, can coexist in patients with IgG4-RD. Therefore, cases of concomitant CAD and IgG4-RD should be accurately diagnosed and evidence should be collected to elucidate the mechanism and characteristics of this condition.

Keywords Immunoglobulin G4-related disease • Coronary artery disease • Coronary computed tomography angiography • Case report

Learning points

- Immunoglobulin G4-related disease (IgG4-RD) is a relatively new disease concept that was first reported as a type of autoimmune pancreatitis in 2001. Most reported cases of IgG4-RD with cardiovascular involvement have included abdominal aortic disease, with coronary artery disease (CAD) being rare.
- We describe a case of CAD, specifically acute coronary syndrome, coexisting with IgG4-RD. Therefore, cases of concomitant CAD and IgG4-RD should be accurately diagnosed and evidence should be collected to elucidate the mechanism and characteristics of this condition.

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Handling Editor: Thomas Johnson

Peer-reviewers: Dejan Milasinovic and Thomas Johnson

Compliance Editor: Mohammed Akhtar

Supplementary Material Editor: Christian Fielder Camm

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a condition that was first reported as a type of autoimmune pancreatitis in 2001.[1] It has gradually been recognized as a chronic fibroinflammatory condition with multiorgan involvement through such manifestations as sialadenitis, thyroiditis, nephritis, lymphadenopathy, and lung disease.[2] Most reported cases of IgG4-RD with cardiovascular involvement have included abdominal aortic disease,[3] with coronary artery disease (CAD) being rare. Here, we present a case of IgG4-RD involving CAD.

Timeline

6 months before admission	No evidence of severe impaired glucose tolerance; blood glucose was 85 mg/dL, and HbA1c was 7.1%.
2 months before admission	Tightness of the chest on exertion
Day of admission	Upon admission, ST-segment elevation myocardial infarction diagnosed and urgent percutaneous coronary intervention performed. Markedly exacerbation of diabetes: blood glucose level, 362 mg/dL and HbA1c, 10.8%.
Hospital Day 3	IgG4-RD diagnosed because of autoimmune pancreatitis and a high serum IgG4 level, 453 mg/dL.
Hospital Day 14	Coronary computed tomography angiography revealed localized wall thickening of coronary artery.
Hospital Day 18	Patient discharged.
9 months after discharge	Coronary angiography did not reveal any restenosis in the stent or any new lesions. Coronary computed tomography angiography found no remarkable changes compared with the findings on primary admission.
19 months after discharge	The follow-up serum IgG4 level had decreased to 330 mg/dL.
20 months after discharge	The diabetes is well controlled with an HbA1c of 7.0% through the administration of insulin. IgG4-RD has spontaneously been recovered without any treatment that includes corticosteroids.

Case presentation

A 74-year-old man with a history of CAD, cerebral infarction, and dyslipidaemia was referred to our hospital with a chief complaint of chest pain and was admitted. The patient had smoked 20 cigarettes per day for 53 years but had stopped smoking 1 year earlier. Physical examination had no significant findings and showed a blood pressure of 154/90 mmHg, a heart rate of 110 b.p.m., and a body temperature of 36.5°C. Electrocardiography showed ST-segment elevation in precordial leads and a depression in inferior leads (*Figure 1*). Laboratory examinations showed elevated troponin levels, with a troponin T level of 0.458 ng/mL. Transthoracic echocardiography revealed impaired left ventricular wall motion in the anteroseptal area, with a left ventricular ejection fraction of 40–45%. A myocardial infarction with ST-segment elevation was diagnosed, and an urgent coronary angiogram revealed thrombotic occlusion of the proximal left anterior descending artery (LAD) (Supplementary material online, *Files*). There was no significant CAD in the left circumflex artery and right coronary artery (RCA). The antiplatelet regime the patient was commenced on at the time of coronary intervention included oral aspirin, 200 mg, and prasugrel, 20 mg.

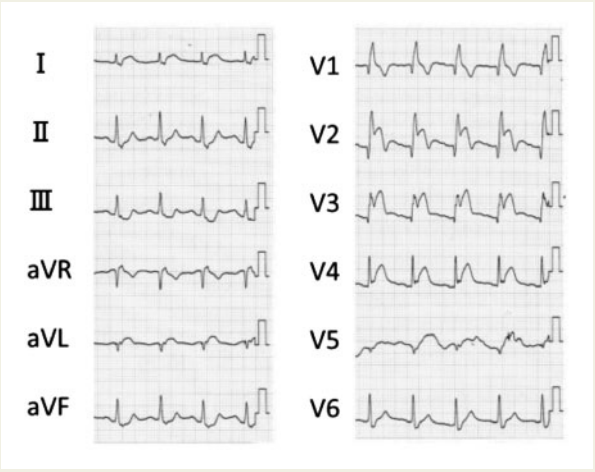

Figure 1 A 12-lead electrocardiogram on admission. ST-segment elevation in precordial leads and a depression in inferior leads.

The patient underwent percutaneous coronary intervention with the implantation of a drug-eluting stent in the LAD (Supplementary material online, *Files*). Importantly, during the present admission of this patient for chest pain, the blood glucose level was high, with a fasting blood glucose level of 362 mg/dL (normal value: 73–109 mg/dL) and haemoglobin A1c level of 10.8% (normal value: 4.9–6.0%). Because, we were told by the patient's previous physician that 6 months earlier the fasting blood glucose level had been 85 mg/dL and the haemoglobin A1c level had been 7.1%, abdominal contrast-enhanced computed tomography (CT) was performed to examine the pancreas. This examination showed diffuse enlargement and a surrounding capsule-like structure. On the basis of these findings, the differential diagnosis included autoimmune pancreatitis. In addition, because autoimmune pancreatitis is a typical finding of IgG4-RD,[1,2] the serum IgG4 level was examined and found to be extremely high (453 mg/dL; normal value: 4.8–105 mg/dL). Therefore, IgG4-RD was diagnosed, despite tissue biopsy not being performed.

Intravascular ultrasonography of the coronary arteries demonstrated mild stenosis of the vascular lumen with an attenuated plaque and the thickening of adventitia in the proximal LAD branch (*Figure 2*).

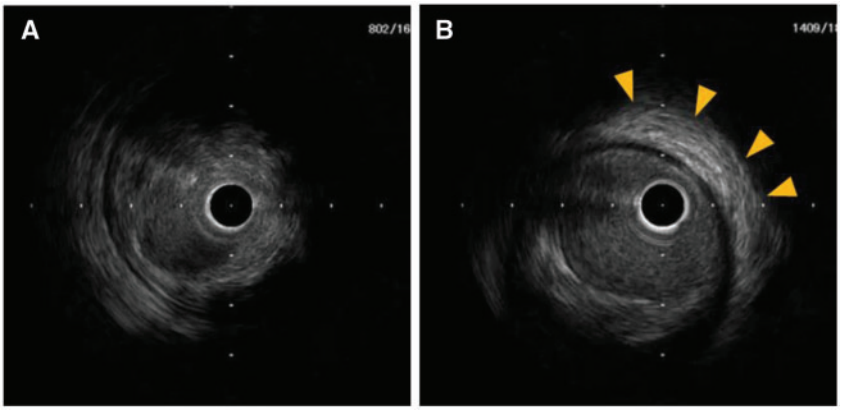

Figure 2 Intravascular ultrasound. Mild stenosis of the vascular lumen with attenuated plaque (*A*). Thickening of adventitia in the proximal left anterior descending artery branch (*B*).

To examine the radiological characteristics of the coronary arteries, coronary computed tomography angiography (CCTA) was performed. A heterogeneous slight thickening was found of coronary artery walls and surrounding soft tissue from the left main trunk through the proximal LAD branch and the proximal RCA. A localized nodular lesion was also observed in the middle of the RCA (*Figure 3*). Coronary angiography also showed mild stenosis of the proximal LAD branch and the proximal RCA and localized mild stenosis in the middle of the RCA (Supplementary material online, *Files*).

To investigate the involvement of other organs in IgG4-RD, gallium scintigraphy was performed. However, gallium accumulation was shown in only part of the pancreas. Contrast-enhanced CT showed only slight thickening of the walls of the thoracic and abdominal aorta, which could not be differentiated from atherosclerotic changes.

With insulin therapy, the blood glucose level was significantly improved. The patient was discharged after 18 days without any complications of CAD. Upon discharge, the patient has closely been followed-up until the present time. The coronary angiogram 9 months after percutaneous coronary intervention did not reveal any restenosis or new lesion. In addition, CCTA performed at the time of coronary angiogram revealed slight wall thickening from the left main trunk through the proximal LAD branch and the proximal RCA. Significant thickening of soft tissue and a coronary aneurysm were not present. There were no remarkable changes compared with the findings of CCTA at the initial presentation.

The medications prescribed on discharge included aspirin, 100 mg once daily; prasugrel, 3.75 mg once daily; rosuvastatin, 5 mg once daily; enalapril, 2.5 mg once daily; bisoprolol, 0.625 mg once daily; insulin glargine, once daily; and insulin lispro, three times a day.

Discussion

After IgG4-RD was first reported, many additional sites have been found, because of high serum levels of IgG4, to be involved.[2] However, little evidence has been reported of the relationship between IgG4-RD and CAD. Therefore, to study the characteristics of CAD in IgG4-RD, we searched the literature and found 15 previously reported cases (Table 1).[4–18]

Among these reported cases, the number of male patients was much higher than that of female patients, with a ratio of 15:1. The reason for male predominance with CAD in IgG4-RD remains uncertain, and the selection bias and an underdiagnosis in female patients could not be excluded. However, in the study by Komiya *et al.*[17] of 10 cases of CAD in IgG4-RD, a high male:female predominance was shown with a ratio of 9:1, which was consistent with our finding. Contrary to the female predominance of general autoimmune conditions, patients with IgG4-RD would more likely be older men, and patients with CAD would also more likely be men. These factors might contribute to the male predominance of IgG4-RD, although more cases and further investigation are required.

In the present case, thickening of coronary artery walls and of soft tissue surrounding several arteries was observed. Because such thickening has also been observed in 13 of 15 previously reported cases (Table 1), it might be a characteristic of CAD in IgG4-RD. Another possible characteristic of CAD in IgG4-RD is mild stenosis of the vascular lumen, which was found in the present case and in five of six previous cases with acute coronary syndrome (ACS) (Table 1).

Cardiac involvement has been reported in cases of IgG4-RD; however, in light of the 15 previously reported cases, ACS is rarely concomitant with IgG4-RD. Instead, the type of cardiovascular involvement most often reported with IgG4-RD has been aortic disease.[3] Interestingly, the features of thickening of coronary artery walls and surrounding soft tissue[19] and of giant coronary artery aneurysm[4] and aortic disease have also been shown in cases of CAD. Furthermore, a pathological perspective suggests that the periarterial thickening and luminal narrowing of the coronary arteries might lead to myocardial ischaemia.[5] These pathological findings appear to be consistent with the present case; however, how the coronary lesion with periarterial thickening and

Table 1 Characteristics of coronary artery disease in reported cases of immunoglobulin-G4–related disease

Reported case	Year	Patient age, years	Sex	Lesion form of coronary artery				ACS	Imaging examinations
				Wall thickening	Soft tissue thickening	Stenosis	Aneurysm		
Nishimura et al.[4]	2016	60	M	no	no	yes	yes	no	CCTA, CAG, TTE
Tanigawa et al.[5]	2012	66	M	yes	yes	yes	no	yes	CCTA, CAG
Matsumoto et al.[7]	2008	63	F	yes	yes	no	yes	no	CCTA, CAG
Ikutomi et al.[8]	2011	75	M	yes	yes	yes	yes	no	CCTA, CAG
Tajima et al.[9]	2014	68	M	unknown	yes	no	no	no	PET-CT, CCTA
Inokuchi et al.[10]	2014	38	M	yes	yes	yes	no	yes (CPA)	CT
Urabe et al.[11]	2012	84	M	yes	yes	yes	yes	yes	CCTA, CAG
Patel et al.[12]	2014	53	M	yes	yes	yes	no	yes (CPA)	autopsy
Guo et al.[13]	2015	88	M	unknown	yes	unknown	no	no	CT
Takei et al.[14]	2012	71	M	yes	yes	yes	yes	no	TTE, CCTA
Keraliya et al.[15]	2016	53	M	yes	yes	yes	yes	yes	CCTA, CAG
Sakamoto et al.[16]	2017	67	M	unknown	yes	yes	no	no	CCTA, CAG
Komiya et al.[17]	2018	59	M	unknown	yes	no	no	no	TTE, CCTA, PET-CT
Bito et al.[6]	2014	69	M	unknown	no	no	yes	yes	CAG, CCTA
Kan-o et al.[18]	2015	68	M	yes	no	yes	yes	no	CT, CCTA
Present Case	2018	74	M	yes	no	yes	no	yes	CAG, CCTA
Total		Mean = 66	M:F = 15:1	10 (63%)	12 (75%)	11 (69%)	8 (50%)	7 (44%)	

ACS, acute coronary syndrome; CAG, coronary angiography; CCTA, coronary computed-tomography angiography; chest CT, computed tomography of chest; CPA, cardiopulmonary arrest; PET-CT, positron emission tomography–computed tomography; TTE, transthoracic echocardiography.

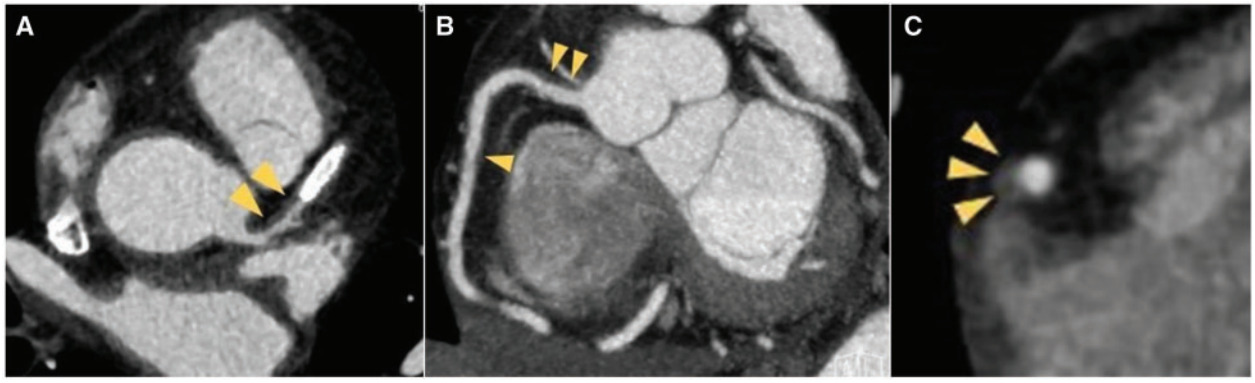

Figure 3 Coronary computed tomography angiography. Heterogeneous thickening of coronary artery wall and surrounding soft tissue in left anterior descending branch (*A*) and the right coronary artery (*B*). Localized nodular lesion in middle of right coronary artery (*C*).

luminal narrowing led to unstable CAD must be clarified. All three previously reported cases of ACS without aneurysm[5,10,12] showed significant stenosis of the vascular lumen; however, the present case showed only mild stenosis. To the best of our knowledge, the present case is the first of ACS in IgG4-RD without an aneurysm or significant stenosis of the vascular lumen.

The present case of IgG4-RD involving CAD was not diagnosed on the basis of tissue biopsy, which is a useful tool for diagnosing IgG4-RD, but on CT findings of heterogeneous thickening of coronary artery walls and concomitant autoimmune pancreatitis, in addition to an elevated serum level of IgG4. Previously reported cases were diagnosed with the following methods (Table 1): eight cases, pathological examination during operative therapy,[5–8] including coronary artery bypass graft,[5–8] or autopsy[9–12]; six cases, CCTA or coronary angiographic findings depicting coronary artery lesions after IgG4-RD was diagnosed in other organs[13–18]; and one case, findings of positron emission tomography CT.[17] These data suggest that CCTA provides useful images for a diagnostic workup, because pathological findings are hard to obtain and cases of IgG4-RD involving CAD can be difficult to diagnose.[15]

With respect to treatment options, a corticosteroid was not administered at this stage of the present case for the following reasons. First, this case of CAD was not associated with findings characteristic of a significant mass, which would respond well to a corticosteroid.[13,16,18] Second, this case had no symptoms, such as jaundice, due to autoimmune pancreatitis. Third, this case was concomitant with severe diabetes. Therefore, careful clinical follow-up should be performed, and corticosteroid therapy might be a reasonable option if coronary lesions progress at a later stage, because this case is most likely due to wall thickening without coronary aneurysm.

The present report suggests that CAD, specifically ACS, can coexist with IgG4-RD. Notably, it is important to clarify that ACS cannot be definitively and directly attributed to IgG4-RD. Therefore, cases of the combination of CAD and IgG4-RD should be accurately diagnosed and evidence should be collected to elucidate the mechanism and characteristics of this condition.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

The authors are grateful to Prof. Masao Okazaki at The Jikei University School of Medicine for his editing contribution.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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