ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–8
https://doi.org/10.1093/ehjcr/ytac153

CASE SERIES
Other

Cardiac manifestations of IgG4-related disease: a case series

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Received 24 November 2021; first decision 17 January 2022; accepted 6 April 2022; online publish-ahead-of-print 8 April 2022

Background IgG4-related disease (IgG4-RD) is an autoimmune condition affecting almost every organ system, with an early inflammatory phase and later fibrotic consequences. Vascular manifestations, particularly, large-vessel involvement in IgG4-RD, are well described. However, important IgG4-related effects on medium-sized arteries and the pericardium are less well recognized. These less frequently reported cardiovascular effects of IgG4-RD include coronary artery stenosis, pericardial disease, cardiac masses, and valvular heart disease.

Case summary This case series focuses on three patients that demonstrate the cardiovascular effects of IgG4-RD and the pitfalls and importance of early diagnosis. Cases 1 and 2 presented with cardiac manifestations prior to more typical organ systems being affected which led to a delay in diagnosis. Case 1 presented with an acute myocardial infarction secondary to IgG4-RD of the coronary arteries and Case 2 presented with pericarditis which progressed to pericardial constriction due to IgG4-RD. Case 3 already had a diagnosis of IgG4-RD from a prior renal biopsy which raised the index of suspicion that his pericardial disease and thoracic mass were also related to IgG4-RD.

Discussion Cardiac manifestations of IgG4-RD remain under-recognized and include coronary artery and pericardial disease. These manifestations often precede more typical manifestations in other organ systems. Recognizing cardiac manifestations of IgG4-RD on cardiac imaging can raise clinical suspicion and act as a catalyst to ascertain a confirmatory diagnosis. Early diagnosis and treatment are crucial to prevent potentially fatal outcomes and irreversible fibrosis.

Keywords IgG4-related disease • Cardiac imaging • Pericardial effusion • Coronary artery disease • Case series

ESC Curriculum 2.3 Cardiac magnetic resonance • 2.4 Cardiac computed tomography • 6.6 Pericardial disease • 2.1 Imaging modalities

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Handling Editor: Christoph Jensen
Peer-reviewers: Ali Nazmi Calik and Rizwan Ahmed
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Learning points

- Cardiac manifestations of IgG4-related disease (IgG4-RD) remain under-recognized and include coronary artery and pericardial disease, cardiac masses, and valvular pathology. These manifestations often precede more typical manifestations in other organ systems.
- Early diagnosis and treatment are crucial to prevent potentially fatal outcomes and irreversible fibrosis.
- Recognizing cardiac manifestations of IgG4-RD on cardiac imaging can raise clinical suspicion and act as a catalyst to ascertain a confirmatory diagnosis.

Introduction

IgG4-related disease (IgG4-RD) is an autoimmune condition that affects almost every organ system and is characterized by an early inflammatory phase followed by later fibrotic sequelae. It most commonly presents with inflammation of the salivary and lacrimal glands, pancreatitis, tubulointerstitial nephritis, and retroperitoneal fibrosis.[1] Vascular manifestations, particularly, large-vessel involvement, are well described.[2,3] However, important IgG4-related effects on medium-sized arteries and the pericardium are less well recognized. These less frequently reported cardiovascular effects include coronary artery stenosis, pericardial disease, cardiac masses, and valvular heart disease.[4] This case series focuses on three patients and demonstrates the cardiovascular effects of IgG4-RD and the pitfalls and importance of early diagnosis.

Timeline

Case 1	Case 2	Case 3
Cardiac presentation: chest pain for 1 h → acute myocardial infarction	Cardiac presentation: presented with dyspnoea for 3 months → diagnosed with pericarditis with significant effusion	Typical organ system affected—kidneys
↓	↓	↓
Four years later: no cardiac symptoms; presented with lacrimal gland enlargement and abdominal pain	One month later: worsening dyspnoea and clinical signs of pericardial constriction. Right heart catheterization and cMRI confirm constriction and pericardial fibrosis	Diagnosis of IgG4-RD confirmed on renal biopsy
'Typical' organ system involved and identified on imaging—lacrimal gland + pancreas	↓	↓
↓		Three years later: presented with dyspnoea and rapid atrial fibrillation. Large pericardial effusion found on TTE
Biopsy of lacrimal gland and pancreas consistent with IgG4-RD	Twelve months later: 'typical' organ system involved and identified on imaging—kidneys and aorta	↓
↓	↓	
IgG and IgG4 sub-class levels elevated	IgG and IgG4 sub-class levels elevated	CMR and PET scan shows pericardial disease and paravertebral mass
↓	↓	↓
CTCA shows soft-tissue masses around coronary arteries involved in AMI	CMR shows residual pericardial thickening but no oedema	Biopsy of paravertebral mass consistent with IgG4-RD
↓	↓	↓
Diagnosis of IgG4-RD made	Diagnosis of IgG4-RD made	Diagnosis of IgG4-RD made
↓	↓	↓
Treatment with prednisone and rituximab	Treatment with prednisone and azathioprine	Treatment with prednisone and rituximab

Case summaries

Case 1

A 55-year-old Caucasian woman presented to hospital with 1 h of chest pain. She was a current smoker with a previous splenectomy and right-sided nephrectomy secondary to trauma and renal cell carcinoma, respectively. She was diaphoretic on arrival to the emergency department but was haemodynamically stable with a normal cardiovascular examination. Initial electrocardiogram (ECG) demonstrated inferior ST-elevation, with subsequent ECGs demonstrating anterior ST-elevation. Her peak troponin was 6889 ng/L (normal <14 ng/L). She underwent emergent percutaneous coronary intervention to her proximal left anterior descending and circumflex arteries. There was a discernible lack of atheroma and an unusual luminal appearance of her coronary arteries angiographically. An autoimmune and vasculitic screen was performed but was negative. She was discharged and remained stable on follow-up.

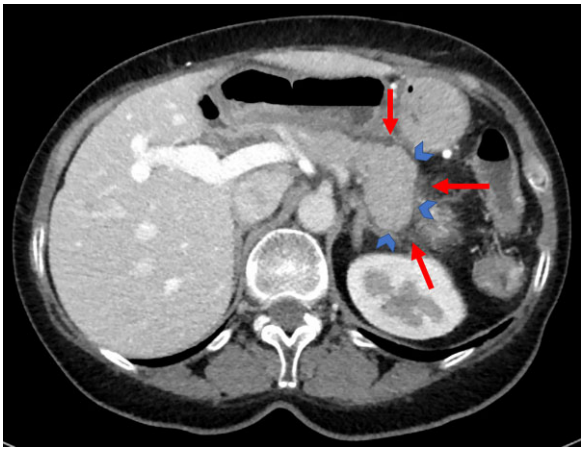

Figure 1 Case 1: Computed tomography abdomen and pelvis showing expansion of the pancreatic tail (arrowhead) and peripancreatic 'halo' (arrow).

Four years later, she concomitantly developed lacrimal gland enlargement and abdominal pain over 6 weeks. Her white cell count and lipase were elevated so a computed tomography (CT) abdomen was performed which showed expansion of the pancreatic tail (*Figure 1*), with her General Practitioner concerned of potential malignancy. Biopsies of her lacrimal gland and pancreatic mass were performed. Histopathological examination of the lacrimal gland biopsy showed a dense inflammatory infiltrate rich in IgG4-positive plasma cells (>100 per high-power field, with an IgG4:polyclonal IgG ratio of >70%), together with dense fibrosis and perivascular inflammation. The pancreatic biopsy similarly showed a dense infiltrate of IgG4-positive plasma cells, patchy storiform fibrosis, atrophy of pancreatic acini, and patchy perivascular inflammation, consistent with IgG4 fibrosclerosing disease (*Figure 2*). Total IgG serum levels were raised at 20.8 g/L (normal range 7.00–16.00 g/L) and sub-class IgG4 severely elevated at 16.3 g/L (normal range 0.03–2.01 g/L). She was diagnosed with IgG4-RD as per the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria.[5] A CT coronary angiogram was organized to assess for IgG4 coronary involvement given her prior unusual

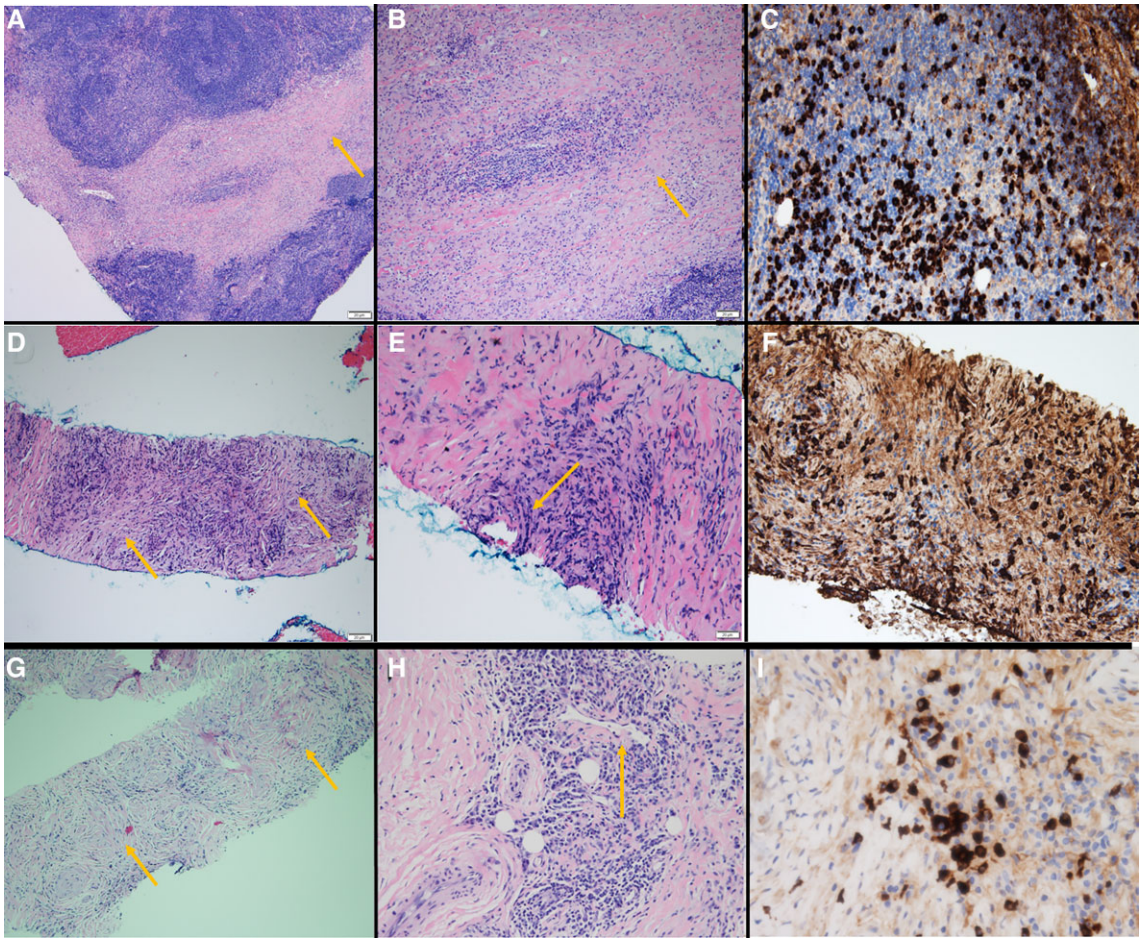

Figure 2 Case 1: Histopathological analysis showing classic features of IgG4 disease including (*A*) storiform fibrosis, (*B*) obliterative phlebitis, and (*C*) dense infiltrate of IgG4-positive plasma cells in the lacrimal gland and (*D*) storiform fibrosis, (*E*) phlebitis, and (*F*) dense infiltrate of IgG4 plasma cells in the pancreatic mass. Case 3: Histopathological examination of paravertebral mass showing classic features of IgG4 disease (*G*) storiform fibrosis, (*H*) dense plasmacytic infiltrate with phlebitis, and (*I*) dense infiltrate of IgG4 plasma cells.

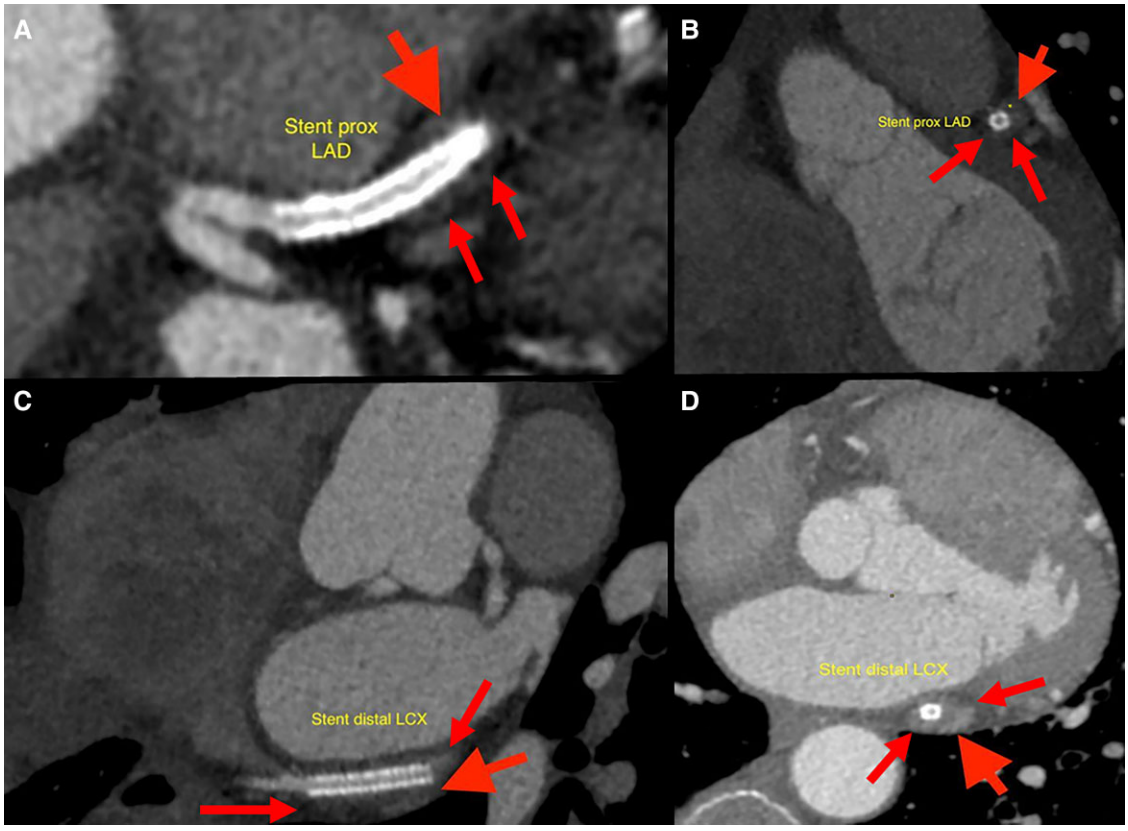

Figure 3 Case 1: Computed tomography coronary angiogram showing circumferential soft-tissue masses surrounding the left anterior descending artery (*A*) (long axis) and (*B*) (transverse) and, circumflex artery, (*C*) long axis and (*D*) transverse.

ST-elevation myocardial infarction (STEMI) presentation. It showed minimal evidence of calcified atheroma; however, there were circumferential soft-tissue masses involving the circumflex and left anterior descending arteries (*Figure 3*), suggesting that her initial STEMI was caused by IgG4-RD. She was treated with oral prednisone, initially commenced at 40 mg before being tapered over the subsequent 6 months to a maintenance dose of 10 mg. She also receives 1 g rituximab infusions currently at 6-month intervals. She had complete resolution of her lacrimal gland enlargement and improvement of her abdominal symptoms. She receives regular collaborative follow-up with her sub-speciality physicians including her cardiologist, immunologist, and gastroenterologist.

Case 2

A 54-year-old middle eastern gentleman, with depression and dyslipidaemia, was admitted to hospital with persistent shortness of breath for 10 weeks, worse on exertion and when lying supine. His cardiovascular examination was unremarkable with no clinical signs of heart failure or pericardial tamponade. The ECG demonstrated inferior T-wave inversion. Transthoracic echocardiogram revealed a moderate pericardial effusion. A CT coronary angiogram revealed marked thickening of the pericardium (*Figure 4A*) but no obstructive coronary stenoses or coronary wall thickening. He was diagnosed with pericarditis and treated with 500 µg colchicine thrice daily, and 400 mg ibuprofen thrice daily. He was re-admitted to hospital 1 month later with clinical signs of constrictive pericarditis. Diagnosis of constriction was confirmed on full heart catheterization. Cardiac magnetic resonance imaging (MRI) illustrated thickened pericardium and increased signal on T2-weighted imaging, suggesting active inflammation with oedema (*Figure 5*). Positron emission tomography (PET) imaging demonstrated uptake in the pericardium (*Figure 6*). An immune and vasculitic screen was negative; however, IgG4 levels were not taken as these are not considered part of routine screening for pericarditis. The immunology team was consulted but could not conclusively find an autoimmune diagnosis based on the investigations performed. Colchicine 500 µg was increased to five times per day and prednisone 50 mg daily was commenced with a weaning regime over 3 months. There was subsequent clinical improvement and reduction in the size of the pericardial effusion.

Twelve months later, the patient presented with anorexia, weight loss, and abnormal liver function tests. The CT chest and abdomen revealed multiple imaging features typical of IgG4 disease including perinephric 'halo', thickening of the aortic wall, and diffuse enlargement of the tail of the pancreas (*Figure 7*). The IgG serum levels were 20.50 g/L (normal range 7.00–16.00 g/L) and IgG4 levels were 8.28 g/L (normal range 0.03–2.01 g/L). Residual pericardial thickening (*Figure 4B*) was noted on CT and cardiac MRI, though

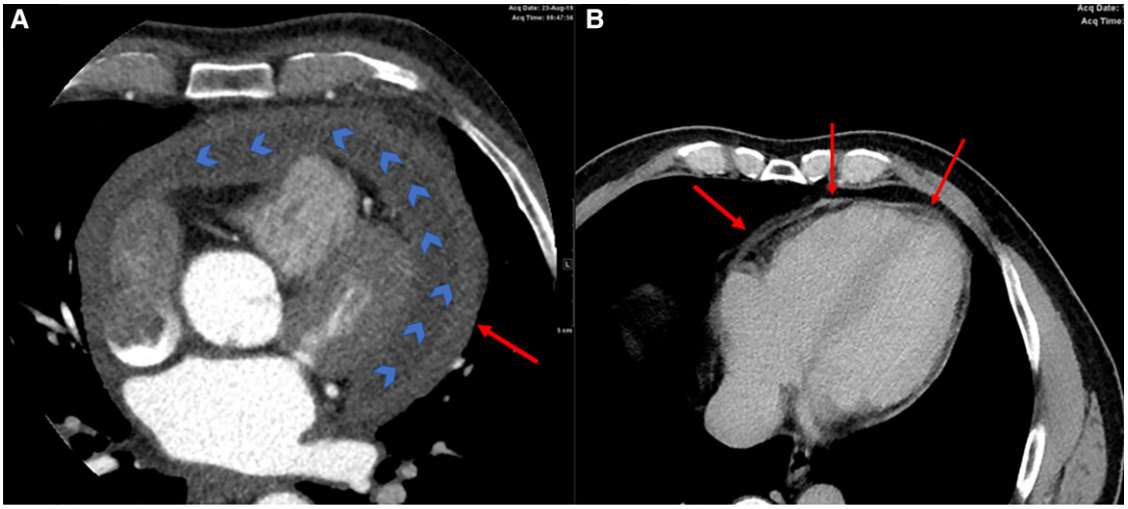

Figure 4 Case 2: Computed tomography chest showing (*A*) marked thickening (arrow) and fluid (arrowhead) within the pericardium; and (*B*) mild residual pericardial thickening (arrow) 12 months later.

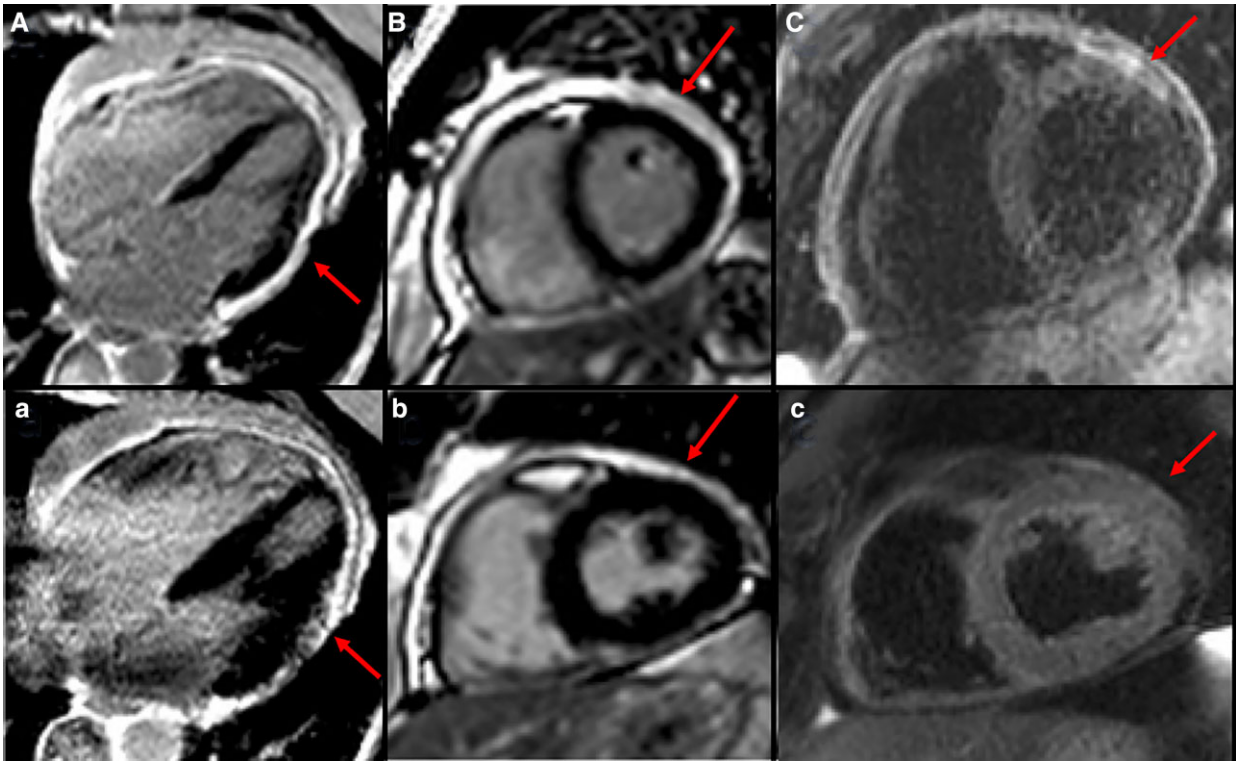

Figure 5 Case 2: Cardiac magnetic resonance imaging illustrating: thickened pericardium with delayed gadolinium enhancement (*A* and *B*) and pericardial oedema (*C*). At 12-month follow-up, there is residual pericardial thickening with delayed gadolinium enhancement (*a* and *b*) but no longer any evidence of pericardial oedema (*c*).

there were improvements in oedema (*Figure 5*). Although no pathology was acquired a diagnosis of IgG4-RD was made according to the ACR/EULAR criteria.[5] The initial presentation with pericarditis was therefore thought to be IgG4-RD. He was re-commenced on 40 mg prednisone, which was weaned over 3 months then ceased, and later commenced on azathioprine with a maintenance dose of 150 mg. This led to symptomatic improvement and a reduction in IgG4 levels from 8.3 to 2.9 g/L. Despite this, residual

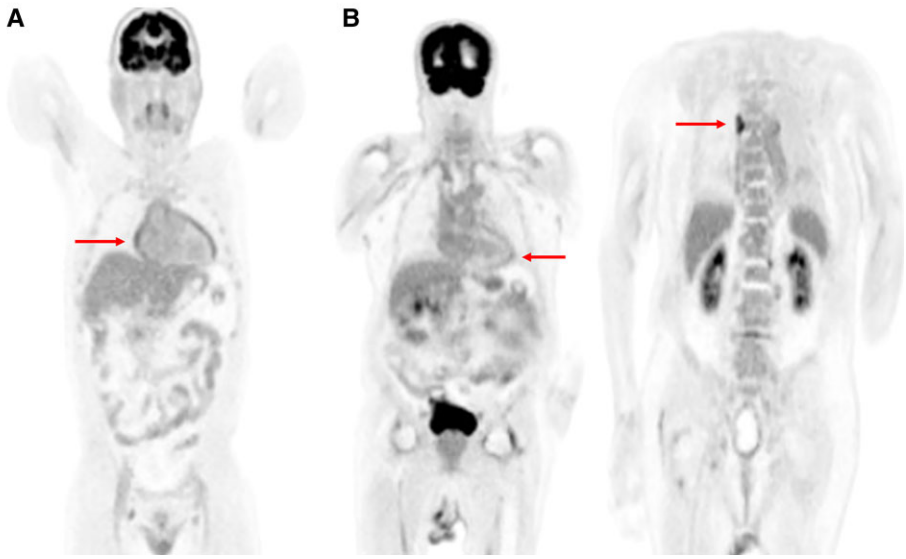

Figure 6 (*A*) Case 2: Positron emission tomography imaging demonstrating uptake in the pericardium, greater than that of myocardium. (*B*) Case 3: Positron emission tomography scan showing moderate glucose uptake in the pericardium (greater than the myocardium) overlying the right ventricle and a separate site of disease in the right paravertebral region of the mediastinum T5.

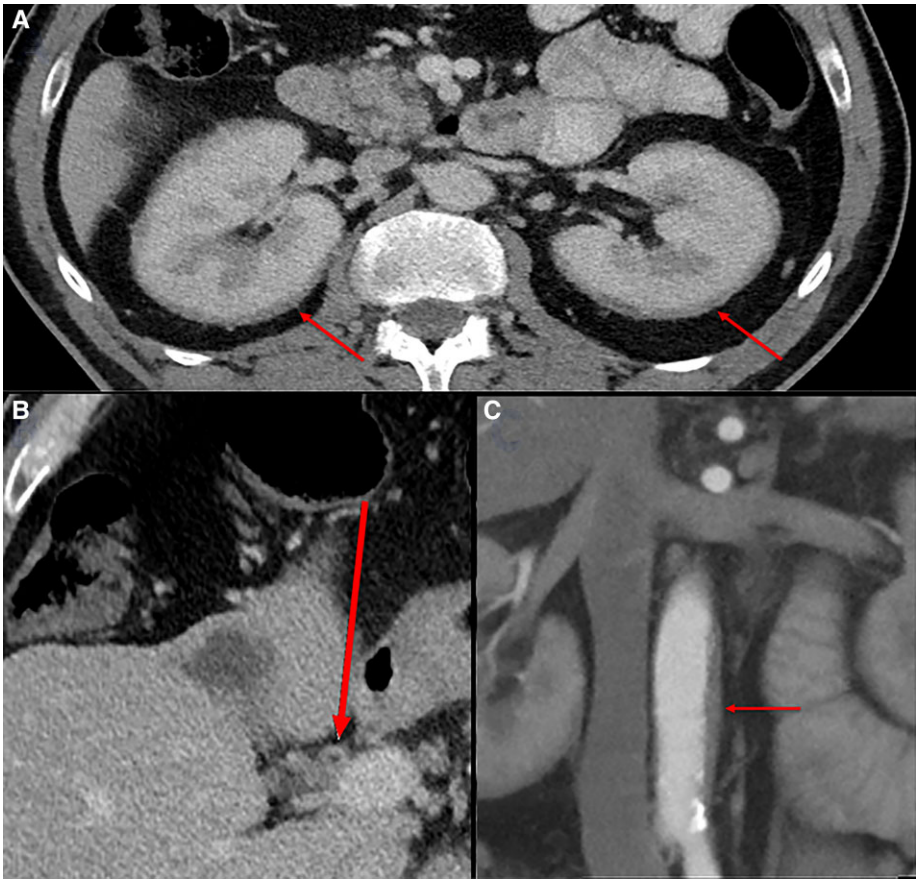

Figure 7 Case 2: Computed tomography chest and abdomen demonstrating (*A*) perinephric 'halo', (*B*) extrahepatic biliary tree enhancement without dilation, and (*C*) thickening of the aortic wall.

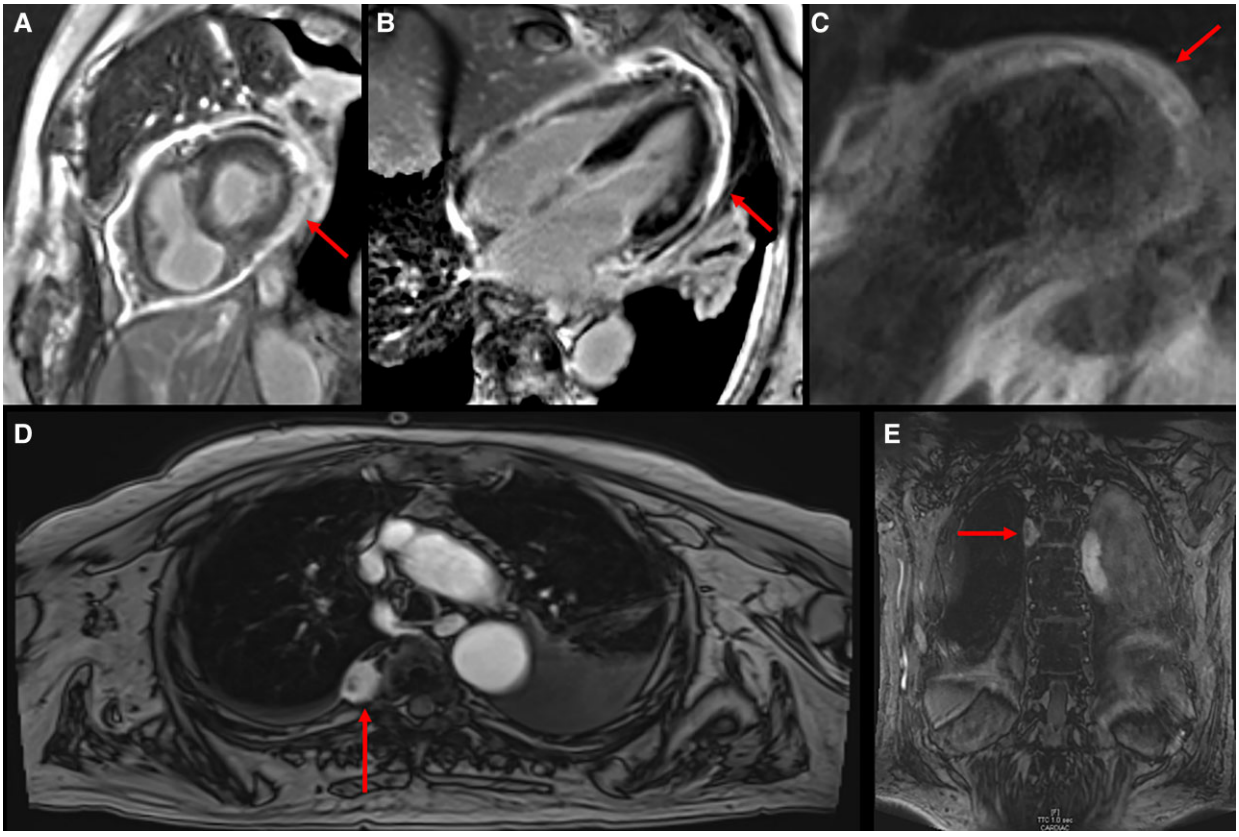

Figure 8 Case 3: Cardiac magnetic resonance imaging illustrating (*A* and *B*) circumferential pericardial thickening up to 5 mm and delayed gadolinium enhancement; as well as pericardial oedema (*C*) on T2-weighted black blood images. The enhancing soft-tissue lesion in the right paravertebral region at the level of T6–7 is demonstrated in (*D*) and (*E*).

pericardial disease remained. Ongoing regular follow-up is overseen collaboratively by his cardiologist, gastroenterologist, and immunologist.

Case 3

An 81-year-old gentleman, of Middle Eastern ethnicity, presented to hospital with a 3-day history of fatigue and vomiting. His background history was notable for chronic kidney disease secondary to IgG4-RD confirmed on renal biopsy (demonstrating tubulointerstitial nephritis and heavy plasmocytic infiltrate positive for IgG4 staining), hypertension, benign prostatic hyperplasia, and popliteal aneurysms. On arrival to hospital, he was hypotensive and in rapid atrial fibrillation. On examination, his blood pressure was 148/52 with no arterial paradox; he was in atrial fibrillation at a rate of 150 beats/min. His jugular venous pressure was elevated to 5 cm and did not alter with respiration. His heart sounds were soft with no murmurs or pericardial rub and his chest was clear. Transthoracic echocardiogram showed a large pericardial effusion, with no signs of tamponade. His heart rate was managed with intravenous digoxin and he underwent a diagnostic and therapeutic pericardiocentesis. The immunology team was consulted to determine whether IgG4 contributed to his presentation. A vasculitic and immune screen was unremarkable. The IgG4 sub-class level was normal (0.95 g/L). The CT coronary angiography was not performed as the patient presented with acute on chronic kidney injury. Cardiac MRI illustrated diffuse pericardial thickening up to 5 mm with pericardial oedema and an enhancing mediastinal soft-tissue lesion in the right posterior paravertebral region at the level of T5 (*Figure 8*). A PET scan showed moderate glucose uptake in the pericardium overlying the right ventricle and a separate site in the right paravertebral region of the mediastinum (*Figure 6B*). Biopsy of the paravertebral mass showed changes consistent with IgG4 fibrosclerosing disease (*Figure 2*). The patient was commenced on prednisone 40 mg daily which was slowly weaned to a maintenance dose of 7.5 mg over 6 months and rituximab infusions (1 g with a plan for 6 monthly infusions). There was a marked clinical response and no evidence of recurrence of his pericardial effusion and remained in sinus rhythm at 3 and 6 months follow-up with both his cardiologist and immunologist.

Discussion

The pathophysiology of IgG4-RD involves an acute inflammatory phase with a waxing and waning course. Early diagnosis and

treatment are critical before the disease reaches its fibrotic phase with irreversible adverse consequences. The diagnosis of IgG4-RD remains challenging, involving a combination of clinical, serological, radiological, and pathological features. The ACR/EULAR criteria, introduced in 2019, requires the involvement of a typical organ and 20 inclusion points to satisfy a diagnosis.[5] Interestingly, the only cardiovascular manifestation of IgG4-RD that is considered 'typical' is involvement of the aorta; thus, the cases described in this series with coronary artery and pericardial involvement would not satisfy this criterion. Instead, diagnosis was dependent on other organ systems meeting the ACR/EULAR criteria which delayed diagnosis.

Cardiac involvement remains under-recognized as a manifestation of IgG4-RD. Case 1 presented with a potentially fatal consequence of IgG4-RD which was not appreciated until years later when typical manifestations became apparent. Recently, IgG4-RD has been identified as a cause of sudden cardiac arrest post-mortem (secondary to coronary artery disease).[6] Case 2 had progressed to the fibrotic stage of disease manifesting in irreversible pericardial constriction before the diagnosis of IgG4-RD was made. Conversely, in Case 3, a diagnosis of IgG4-RD already existed, though of note IgG4 levels were normal. This led to a clinical awareness that the pericardial disease may be a cardiac manifestation of this condition, allowing prompt diagnosis.

Cardiac imaging plays a role in raising the index of suspicion of IgG4-RD. Coronary artery involvement is characterized by periarterial wall thickening and circumferential soft-tissue swelling readily seen on CT coronary angiography.[7] Pericardial involvement can be identified on transthoracic echocardiography and CT imaging of the chest. Cardiac MRI (which demonstrates fibrosis) and FDG-PET imaging (which demonstrates active disease and helps to guide biopsies) are useful in establishing a diagnosis but remain non-specific.[2,4,7] When IgG4-RD is suspected, further investigations including serology, imaging of other organ systems, and biopsies can be performed.

Conclusions

Cardiologists and other sub-speciality physicians must leave their 'individual specialty silos' to have a high index of suspicion for this condition and work collaboratively to confirm a diagnosis. Failure to do so can lead to delayed treatment, which, as highlighted in this case series, can have potentially fatal acute or long-standing fibrotic consequences.

Lead author biography

Dr Seshika Ratwatte completed her cardiology training at Concord Repatriation General Hospital in Sydney Australia. She is currently completing her PhD and has research interests in pulmonary hypertension, epidemiology and cardiac imaging.

Supplementary material

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

Acknowledgements

There are no acknowledgments to be declared.

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

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: There are no sources of funding to be declared.

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