ESC European Society of Cardiology

European Heart Journal - Case Reports (2024) **8**, ytae620
https://doi.org/10.1093/ehjcr/ytae620

CASE REPORT
Heart failure

Immunotherapy-mediated myocarditis and concurrent vasospastic angina in a patient with established ischaemic heart disease: a case report

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Received 5 March 2024; revised 12 May 2024; accepted 1 November 2024; online publish-ahead-of-print 19 November 2024

Background Immunotherapy has become a pillar of modern oncological management but is associated with significant immunotherapy-related adverse events (IRAEs). While myocarditis is a prominent IRAE which clinicians are increasingly aware of, immunotherapy-related coronary vasospasm is far less appreciated and can be especially difficult to elucidate in pre-existing coronary artery disease. This case demonstrates the approach to diagnosis and management of multiple cardiovascular and non-cardiovascular IRAEs.

Case summary A 57-year-old male with a history of metastatic melanoma on combined immunotherapy and ischaemic heart disease with multiple previous percutaneous coronary interventions presented with typical chest pain and troponin rise. Differential diagnoses for this presentation included a non-ST elevation myocardial infarction, myocarditis, and coronary vasospasm. Coronary angiogram did not reveal any new significant obstructive coronary artery disease while cardiac MRI did not reveal any radiological features consistent with myocarditis. However, empirical treatment for IRAEs resulted in both clinical and biochemical improvement and ability to discharge the patient on steroids and coronary vasodilators, having been GTN-infusion dependent as an inpatient.

Discussion Cardiovascular IRAEs are important to be aware of when managing patients on immunotherapy and more than one IRAE can occur concurrently. Given the caveats of non-invasive imaging and invasive nature of endomyocardial biopsy, the clinical history is key in establishing these crucial diagnoses which will significantly impact ongoing oncological management.

Keywords Case report • Cardio-oncology • Immunotherapy-related adverse events • Myocarditis • Coronary vasospasm • Cardiac MRI

ESC curriculum 2.3 Cardiac magnetic resonance • 2.1 Imaging modalities • 6.9 Cardiac dysfunction in oncology patients • 6.5 Cardiomyopathy

Learning points

- It is important to have a high clinical suspicion of cardiovascular immune-related adverse effects for patients on immunotherapy which may include, but is not exclusively, myocarditis.
- The clinical history is key in establishing these diagnoses as there are caveats to invasive and non-invasive diagnostic procedures.

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Handling Editor: Diego Araiza-Garaygordobil
Peer-reviewers: Albert Galyavich; Cuiro Santoro; Diego Araiza-Garaygordobil
Compliance Editor: Maria Isabel Gonzalez del Hoyo

Introduction

The landscape of management of various malignancies has changed dramatically in the last few years with the increasing use of immune checkpoint inhibitors (ICIs), namely programmed cell death-1 (PD-1) inhibitors and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors. However, the advent of these new therapies has also led to the recognition of significant immunotherapy-related adverse events (IRAEs).[1–3] In this report, we present a novel case of multiple concurrent cardiovascular and non-cardiovascular IRAEs which provided several challenges in terms of diagnosis and management.

Summary figure

Day of Admission	D1	D2	D3	D4	D5	D6	D7	D8	D9
Chest pain	Yes	Yes	Yes	Yes	Yes	Yes	Improved	Resolving	No
Troponin	238 → 205	181 → 184	166	386 → 370	355	246	169	135	
BNP								735.9	
Procedures	Echocardiogram Cardiac MRI		Coronary angiogram						
Medical Therapy									
Opiates	Fentanyl 75mcg	Fentanyl 25mcg Morphine 5mg	Fentanyl 75mcg Morphine 12.5mg	Fentanyl 25mcg	Fentanyl 25mcg				
GTN SL	0.9mg	1.2mg	2.4mg	4.8mg	19.2mg	3.3mg	2.1mg	2.4mg	
GTN patch	10mg/24hr	10mg/24hr	5mg/24hr	5mg/24hr					
GTN IV					Yes	Yes Weaned 4hrs	Yes Weaned off		
Antianginal therapy	Bisoprolol 7.5mg ISMN 30mg	Bisoprolol 7.5mg	Bisoprolol 7.5mg Amlodipine 5mg	Bisoprolol 7.5mg Amlodipine 5mg	Bisoprolol 10mg Amlodipine 7.5mg ISMN 60mg Nicorandil 20mg	Bisoprolol 10mg Amlodipine 7.5mg ISMN 120mg Nicorandil 20mg	Bisoprolol 10mg Amlodipine 7.5mg Diltiazem 180mg ISMN 120mg Nicorandil 20mg	Diltiazem 180mg ISMN 120mg Nicorandil 20mg	Diltiazem 180mg ISMN 120mg Nicorandil 20mg
Steroids			PO Pred 50mg	PO Pred 50mg	PO Pred 50mg	PO Pred 50mg IV Methylpred 1g	IV Methylpred 1g	IV Methylpred 1g	PO Pred 100mg

Case presentation

A 57 year-old Caucasian male was admitted to a regional hospital with typical cardiac chest pain. He had a non-ST elevation myocardial infarction 18 months ago, and coronary angiography demonstrated an occluded right coronary artery (RCA) and severe stenosis of the proximal left anterior descending (LAD) artery. This necessitated coronary artery bypass grafting with a left internal mammary artery (LIMA) graft to his LAD, and a left radial artery (LRA) graft to his posterior-descending artery (PDA). His other medical history was significant for multiple previous percutaneous coronary interventions (PCI) to his RCA and LAD (see Supplementary material online, *Table S1*), hypertension, ex-smoker status, and a recent diagnosis of BRAF V600k mutation metastatic left occipital melanoma.

His pre-admission medications included: aspirin 100 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, bisoprolol 7.5 mg daily, ezetimibe 10 mg daily, isosorbide mononitrate (ISMN) 30 mg daily (commenced on index admission to the peripheral hospital 48 h prior to transfer to our centre), ramipril 2.5 mg daily, and as needed sublingual glyceryl trinitrate (GTN). Notably, he had recently commenced immune checkpoint inhibitors [nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor)] with the first and only dose having been administered 20 days prior to his presentation.

The patient initially presented with typical cardiac chest pain. He was haemodynamically stable and had an unremarkable examination and was euvolaemic. His electrocardiogram (ECG) demonstrated sinus rhythm with inferior Q waves, and his initial high sensitivity troponins (TnI) were 56 and then 52 ng/L (noting a baseline of 12 ng/L just a few weeks prior). He had further episodes of pain and TnI elevation to 238 ng/L, prompting transfer to our quaternary cardiac centre. The chest pain was exquisitely responsive to sublingual GTN and the ECG during episodes of pain demonstrated frequent ventricular ectopy (*Figures 1* and *2*).

Additionally, the patient had reported throat fullness, weight loss, and palpitations. There was biochemical evidence of hyperthyroidism with a TSH < 0.01 mIU/L, free thyroxine > 78.8 pmol/L, and free T3 44.4 pmol/L (normal range 3.2–6.1). A diagnosis of severe immunotherapy-mediated thyroiditis and possible myocarditis was made. In discussion with Endocrinology, treatment with oral prednisolone 50 mg daily and oral carbimazole 15 mg three times daily was initiated. However, he continued to experience recurrent severe episodes of chest pain requiring escalating doses of GTN and morphine (see *Summary figure*). Cardiac MRI (CMR) demonstrated a normal LV size with low-normal LV ejection fraction and evidence of previous non-LAD territory infarction but no new evidence of myocardial fibrosis or oedema.

Coronary angiography demonstrated severe native coronary artery coronary artery disease but widely patent grafts (*Figure 2*). The only interval change from his previous angiogram was an 80% proximal stenosis in a small calibre (<2.0 mm) ramus intermedius artery. Balloon dilatation was attempted but unsuccessful and therefore further attempts at PCI were abandoned. He developed further typical chest pain intraprocedurally unrelated to PCI which was associated with frequent ventricular ectopy without ST segment changes. Although coronary artery spasm was not seen at the time of angiography, this was strongly supported by the clinical history and responsiveness to nitrates. The patient had ongoing chest pain, with further elevation in TnI to 386 ng/L and BNP 735.9 ng/L, which required commencement of a GTN infusion (initial rate 30 μg/min) that was difficult to wean due to pain recrudescence. He was also commenced on coronary vasodilators (amlodipine 5 mg daily and ISMN 60 mg daily).

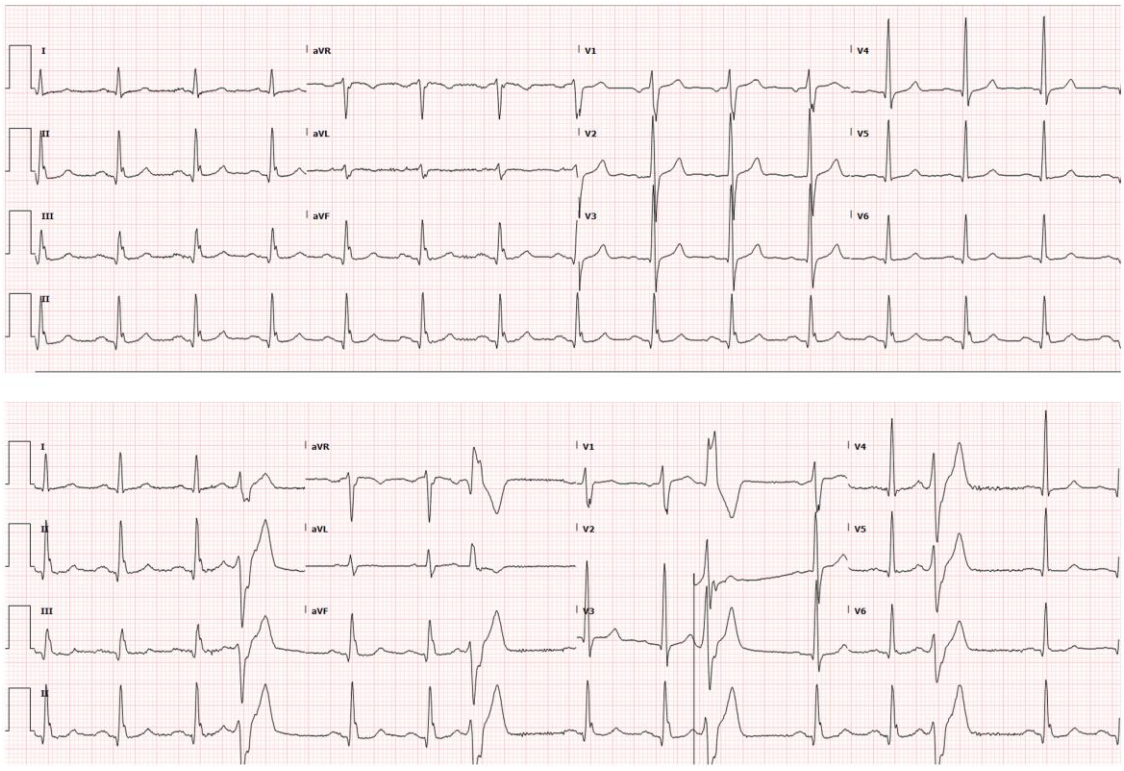

Figure 1 Baseline electrocardiogram (ECG) on arrival to our centre demonstrating normal sinus rhythm with inferior Q waves (top) and ECG with chest pain the next day demonstrating frequent ventricular ectopy (bottom).

He was reviewed by the cardio-oncology team and the impression was that of ICI-related myocarditis with concurrent coronary vasospasm. Intravenous methylprednisolone 1 g was administered daily for 3 days, and bisoprolol and amlodipine were replaced by modified-release diltiazem 180 mg daily. This resulted in 1 day of off-label dual calcium channel blockade as he was transitioned from a non-dihydropyridine to a dihydropyridine calcium channel blocker. Within 48 h, he was completely weaned off the GTN infusion and his TnI decreased to 169 ng/L. He was discharged on Day 10 of his admission on oral prednisolone 100 mg daily weaning by 10 mg per week, carbimazole 15 mg three times daily, modified-release diltiazem 180 mg daily, ISMN 120 mg daily, and nicorandil 10 mg twice daily. At three month follow-up, he had no recurrence of chest pain and troponin remained mildly elevated (30–35 ng/L) with normalization of his BNP. He had an admission for chest sepsis two months after discharge and continues to follow-up with a specialist oncology centre and our cardio-oncology clinic (*Figure 3*).

Discussion

This case report highlights the challenges facing physicians who are treating patients with ICI therapy, and the management of cardiovascular IRAEs. A systematic review in 2020 suggested that atrial fibrillation was the most common cardiovascular IRAE (4.6% of patients) whilst myocarditis was reported to have an incidence of 0.04–1.14%.[4–6] The major adverse cardiovascular event rate of ICI-related myocarditis is 50%, and these rates are higher in patients treated with combination therapy.[2,4] Mortality associated with cardiovascular IRAEs has been reported as high as 37.9%.[2] ICI-related myocarditis should be considered early in the treatment regimen with the median time of onset from the first dose of immunotherapy of 27–65 days, while late presentations at up to 454 days have also been reported.[2,5–7]

Diagnosis of ICI-related myocarditis is suspected based upon clinical history, and is usually confirmed with serum troponin levels and non-invasive imaging.[6] The gold standard in diagnosis remains a positive endomyocardial biopsy (EMB) which alone can meet the pathohistological criteria for myocarditis, however, this is invasive and not widely available. CMR features of myocarditis based on the Lake Louise criteria, coupled with a serum troponin elevation, can meet the clinical diagnostic criteria for ICI-related myocarditis.[6,8] In our case, the patient did not have a myocardial biopsy and did not meet major clinical diagnostic criteria, however he did meet the minor clinical diagnostic criteria with a new troponin elevation, a clinical syndrome consistent with myocarditis and the presence of another significant IRAE (thyroiditis). We acknowledge that the diagnosis of ICI-related myocarditis based on minor criteria has not been validated in clinical studies and we were cautious to make this diagnosis as it resulted in a significant interruption to his oncological management. However, it was felt that the risk of clinical deterioration and further myocardial injury was higher than the benefit of continuation of immunotherapy. As such, this diagnosis was made in conjunction with our interventional cardiology and cardio-oncology teams, as well as his treating oncologist.

Despite the increased use of CMR, it is important to appreciate that up to 50% of EMB-confirmed myocarditis patients may have no positive CMR findings.[7] Numerous reasons have been postulated for this, including that CMR may have been performed too early in the disease process or may lack sensitivity in mild troponin elevations.[9,10] Our patient had a CMR performed after 3 days of symptoms and within 1 day of his transfer to our centre. Zhang *et al.*[9] demonstrated that suspected

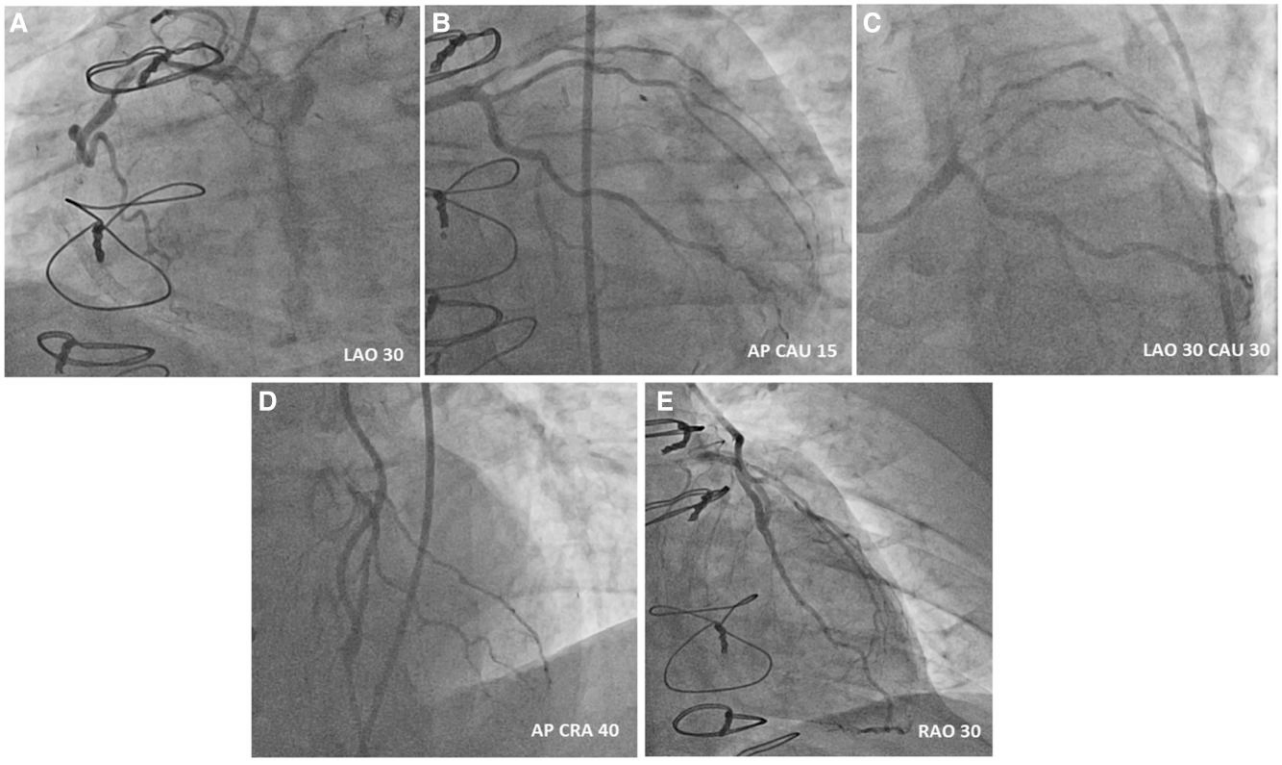

Figure 2 Coronary angiogram demonstrated severe proximal RCA stenosis with occlusion in the mid-vessel (*A*) and a chronic total occlusion of the LAD with a severe stenosis in the proximal ramus intermedius artery which is a small calibre vessel < 2 mm, noting 6 French catheter for reference (*B* and *C*). Graft study demonstrated that the LIMA–LAD and LRA–RPDA grafts were widely patent (*D* and *E*). LAD, left anterior descending artery; RCA, right coronary artery; LIMA, left internal mammary artery; LRA, left radial artery; RPDA, right posterior-descending artery.

myocarditis patients who had a CMR performed at least 4 days into the admission had significantly higher rates of LGE compared to those who had an earlier CMR (72.0% vs. 21.6%, respectively, $P < 0.001$). With regard to management, ESC guidelines suggest cessation of ICIs in all suspected or confirmed cases and once confirmed, steroid therapy is suggested. The decision regarding weaning steroids and continuation of ICIs post-recovery should be made in a cardio-oncology multidisciplinary team.[6]

While ICI-related myocarditis is a more established clinical entity, ICI-related coronary vasospasm is far less appreciated and has only been detailed in a handful of case reports with an unclear pathophysiology.[10–13] In this case, vasospasm represented the most significant symptom burden for our patient. Given its rarity, there are no guidelines for the management of ICI-related coronary vasospasm. The diagnosis was made due to recurrent typical chest pain associated with ventricular ectopy which was nitrate-responsive in the absence of significant new obstructive coronary artery disease. Moreover, pulsed methylprednisolone therapy enabled cessation of the GTN infusion, implicating ICIs in this disease process. We acknowledge that beta-blockers were continued earlier in this case which can exacerbate vasospasm. This choice was made as a consensus opinion on the diagnosis of ICI-related vasospasm was required before altering his medical management of ischaemic cardiomyopathy for which beta-blockers were indicated. Once the diagnosis of ICI-related vasospasm was confirmed, the beta-blocker was ceased for calcium channel blockade alone which resulted in further clinical improvement.

We acknowledge that there are a few limitations of this case. First, obstructive coronary artery disease due to the severe ramus intermedius artery stenosis is a valid and more common differential diagnosis for this presentation. However, given the aforementioned clinical picture with post-procedural pain and exquisite response to steroid therapy, we felt that this was more in keeping with ICI-related coronary vasospasm rather than obstructive coronary disease in the small calibre ramus intermedius branch that subtended a small area of myocardium. Second, no provocation testing was performed during the diagnostic coronary angiogram as this was performed urgently out of hours. Third, no EMB was performed as it was felt that the risk–benefit of this procedure was not justified in this case given its low sensitivity and no specific site for biopsy based on CMR. Finally, ICI-related vasculitis is also a valid differential diagnosis in this case and would likely be responsive to steroid therapy, however we felt that the episodic nature of his pain and responsiveness to vasodilators in particular made vasospasm more likely.

In conclusion, this case report is the first, to our knowledge, to describe concurrent immune checkpoint inhibitor-related myocarditis, coronary vasospasm, and thyroiditis. While ICI-related myocarditis is an established clinical entity, the diagnostic criteria as guided by non-invasive imaging is imperfect and a strong clinical suspicion is warranted. The complexity in this case arose due to the presence of ischaemic chest pain more in keeping with coronary vasospasm which improved with steroid therapy, consistent with an immunotherapy-driven process. This case highlights the importance of clinical acumen in the absence of confirmatory diagnostic tests, as well as the early involvement of a multidisciplinary team including a cardio-oncologist where possible to guide management.

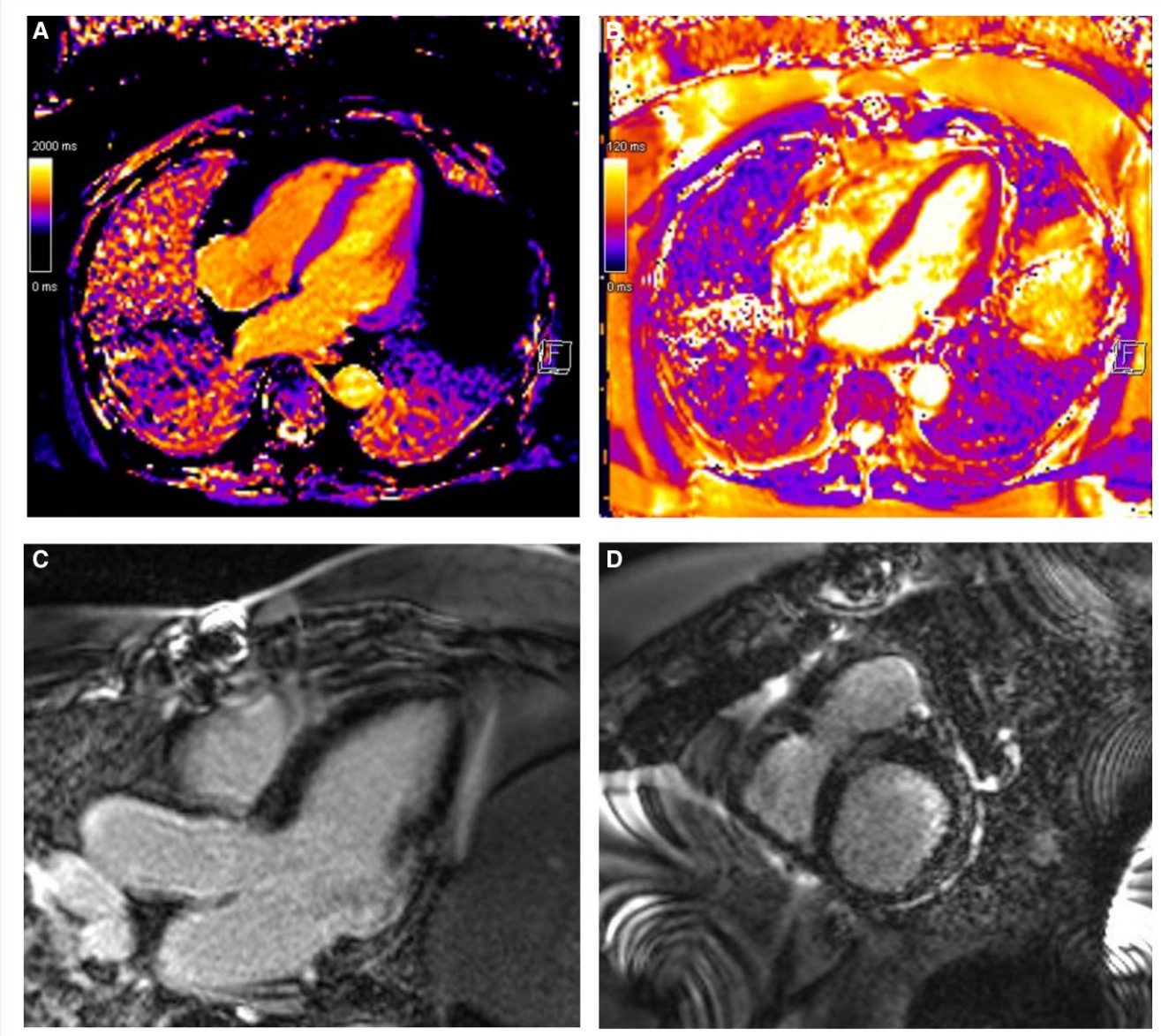

Figure 3 Cardiac MRI demonstrating normal global native myocardial T1 (*A*) and T2 (*B*) values with no regional variation. This study revealed normal left ventricular size with low-normal left ventricular ejection fraction (51%) with a previous infarcted territory in the basal inferior and basal posterior segments as demonstrated by akinesis and late gadolinium enhancement in the three-chamber (*C*) and short axis (*D*) late gadolinium series.

Lead author biography

Jefferson Ko graduated from Monash University with MBBS (honours) and is currently a second year cardiology advanced trainee at the Victorian Heart Hospital in Melbourne, Australia. He is interested in all aspects of cardiology, most notably advanced heart failure, as well as the intersection between cardiology and other medical specialties as seen in this current work as well as previous work in the liver transplantation field.

Supplementary material

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

Consent: The authors confirm that the patient provided informed consent for publication of this case report in keeping with COPE guidelines.

Conflict of interest: None declared.

Funding: No additional funding was obtained.

Data availability

The data that support the findings of this study are available from the authors upon reasonable request.

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