

Left ventricular systolic dysfunction with concomitant bradyarrhythmia in a patient with POEMS syndrome: a case report

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Background

POEMS syndrome (PS) is a paraneoplastic disorder from plasma cell dyscrasia, characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes. Vascular endothelial growth factors (VEGFs)-driven fluid extracellular matrix expansion plays a key role in this condition. Associated cardiac involvement has been sparsely reported thus far.

Case summary

A 55-year-old woman with PS presented with a pleural effusion and respiratory failure requiring mechanical ventilation. Transthoracic echocardiogram revealed left ventricular (LV) systolic dysfunction with a moderate pericardial effusion. She developed intermittent complete heart block and ventricular standstill, requiring temporary transcutaneous pacing. Further evaluation revealed no significant coronary stenosis on coronary angiogram and cardiac magnetic resonance (CMR) showed elevated T1 and extracellular volume suggestive of myocardial oedema with possible early cardiac infiltration. She had a dual-chamber permanent pacemaker implanted in view of recurrent high-grade heart block. She was initiated on a daratumumab-based chemotherapy regimen prior to discharge. She recovered well subsequently with a promising clinical response to chemotherapy.

Discussion

We describe the first case of LV systolic dysfunction with concomitant significant bradyarrhythmia in a patient with PS. CMR revealed evidence suggestive of LV myocardial oedema and/or possible early infiltration. VEGF overexpression could explain oedema-related LV dysfunction which reversed with adequate diuresis, as well as damage to the conduction system. Early cardiac amyloidosis, which can be associated with PS, is an important differential diagnosis. Pacemaker implantation, adequate diuresis, and definitive chemotherapy are key to the management of concomitant ventricular myocardial and electrical dysfunction in such rare case.

Keywords

POEMS syndrome • Bradyarrhythmia • Complete heart block • Conduction system abnormality • Systolic dysfunction • Case report

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Learning points

- Progressive POEMS syndrome (PS) can cause serious ventricular systolic dysfunction with concomitant bradyarrhythmia or conduction system abnormalities.
- Use of cardiac telemetry monitoring and cardiac imaging tools is crucial in the evaluation and management of conduction system and myocardial contractile dysfunction in PS.
- Bradycardia pacing therapy and optimal medical therapy including diuresis and chemotherapy are part of the current treatment strategy for cardiac sequelae in PS.

Introduction

POEMS syndrome (PS) is a rare paraneoplastic disorder due to plasma cell dyscrasia. It is characterised by the presence of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes.¹ Cytokines like vascular endothelial growth factor (VEGF) are released in large amounts.² Rare cardiac involvement had been reported, mainly attributed to VEGF overexpression with endothelial, myocardial and pulmonary vascular dysfunction and consequent heart failure and pulmonary hypertension.^{3–5} Conduction system abnormalities are also reported.⁶ Treatment response in PS is variable and cardiac involvement may portend worse outcomes.^{4,6} We report a case of progressive PS who presented with both ventricular systolic dysfunction and significant bradyarrhythmia requiring permanent pacing therapy. To our best knowledge, this is the first case describing the clinical presentation and management of coexisting myocardial contractile and electrical dysfunction in a patient with PS.

Timeline

Case presentation

A 59-year-old female with history of presumptive chronic inflammatory demyelinating polyneuropathy developed further abnormalities in other organ systems. She fulfilled the diagnostic criteria of PS: polyneuropathy, monoclonal gammopathy, elevated VEGF levels ([Table 1](#)), sclerodermoid skin features, subclinical hypothyroidism, and extravascular volume expansion. She was started on lenalidomide and dexamethasone.

A few months later, she developed progressive dyspnoea and presented with hypoxaemic respiratory failure for which she received urgent intubation and mechanical ventilation. Physical examination revealed decreased air entry that was more prominent over the right lung field than the left on auscultation with bilateral lower limb oedema. Her abdomen was also distended. Chest radiography showed an asymmetrically larger right-sided pleural effusion, cardiomegaly with upper lobe diversion ([Figure 1](#)). A 12-lead electrocardiogram showed normal sinus rhythm with subtle ST depressions in the inferolateral leads and small QRS complexes in the limb leads ([Figure 2A](#)). High-sensitivity troponin was slightly elevated with no

Timeline	Event
1 year prior	Polyneuropathy due to possible chronic inflammatory demyelinating disease and started on immunosuppressant
4 months prior	Fulfilled criteria of POEMS syndrome and started on lenalidomide and steroids
During presentation	Intubated and mechanically ventilated for hypoxaemic respiratory failure due to volume overload state and started on intravenous diuretics
Day 3–4	Developed intermittent complete heart block noted on cardiac telemetry monitoring and placed on transcutaneous cardiac pacing
Day 6	Worsening right pleural effusion drained
Day 7	Extubated and changed to nasal prongs Transthoracic echocardiography showed depressed left ventricular ejection fraction (35%) with a moderate pericardial effusion without tamponade
Day 14	Coronary angiogram showed no significant stenosis An episode of ventricular standstill prior to angiogram
Day 17	Cardiac magnetic resonance imaging showed elevated native T1 and extracellular volume fraction values, without delayed gadolinium enhancement in the left ventricular myocardium
Day 18	Decision made for implantation of dual-chamber cardiac pacemaker insertion for high-grade atrioventricular (AV) block
Day 19	Repeat transthoracic echocardiogram showed normalized systolic function with reduced pericardial effusion after diuresis
Day 21	Daratumumab/dexamethasone initiated
Day 30	Discharged with a course of maintenance diuretics, fluid restriction advice and daratumumab-based treatment regimen Outpatient Cardiology and Haematology follow-up arranged
5 months later (outpatient)	PPM device interrogation showed normalisation of AV conduction (0% ventricular pacing) Clinical response seen with daratumumab-based treatment

Table 1 Laboratory data during diagnosis of POEMS syndrome (shaded)

Test	Unit (ref)	August 2019	October 2019	December 2019	February 2020	March 2020	April 2020	September 2020
VEGF	pg/mL (<96.2)	381						199
Total IgA	g/L (1.2–4.4)	8.2	8.2	6.7		9.4	6.2	
Kappa FLC	mg/L (3.3–19.4)	14.1	17.7	16.4	24.8	38.1	11.5	3.3
Lambda FLC	mg/L (5.7–26.3)	67.9	96.8	80.9	84.8	127.9	74.6	22.5
Free kappa/lambda ratio	(0.26–1.65)	0.21	0.18	0.20	0.29	0.30	0.15	0.15
Troponin	ng/L (0–18)					356	17	
BNP	pg/mL (0–100)					54		

Laboratory trend showing progression of POEMS syndrome till admission. Clinical response seen after daratumumab-based treatment initiation.

BNP, brain natriuretic peptide; IgA, serum immunoglobulin A; Kappa FLC, serum Kappa free light chain; Lambda FLC, serum Lambda free light chain; VEGF, vascular endothelial growth factor.

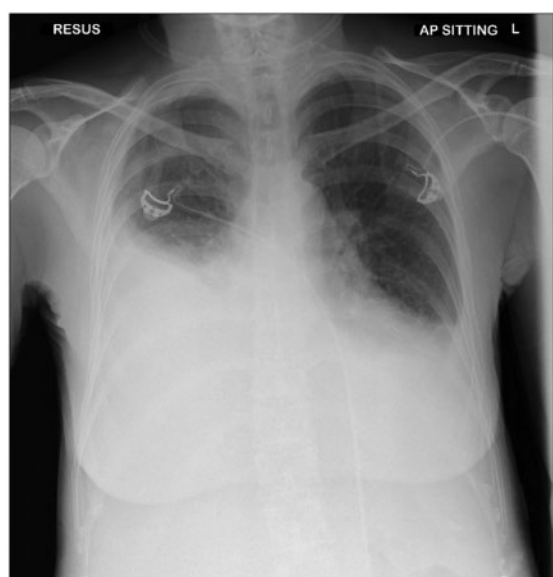


Figure 1 Chest radiograph demonstrating asymmetrical right pleural effusion with cardiomegaly and pulmonary congestion.

significant delta change. Brain natriuretic peptide was normal. The full blood count and renal panel were both unremarkable.

She was started on intravenous diuretics and underwent right-sided pleural drainage. Whilst being intubated, she developed an episode of intermittent complete heart block with slow narrow complex escape, the longest duration lasting 30 min, without any precipitating events or prior rate-lowering medications (Figure 2B). Intravenous noradrenaline was started for haemodynamic stabilisation. Transcutaneous pacing pads were placed on her for temporary pacing support. She required high pacing burden for the first 2 days before she recovered intrinsic atrioventricular (AV) conduction and sinus rhythm thereafter. Transthoracic echocardiogram revealed globally depressed left ventricular (LV) ejection fraction (35%) with a moderate pericardial effusion without features of cardiac tamponade. The pulmonary pressure was not elevated (Figure 3). She was

subsequently extubated after adequate diuresis and drainage of the right pleural effusion and transferred to the general ward with close continuous cardiac telemetry monitoring, assessing for further heart block.

She remained stable post-extubation without further arrhythmias and did not require additional cardiac monitoring. However, just prior to her coronary angiogram, she developed an episode of ventricular standstill lasting for approximately 1 min which needed transcutaneous pacing support. The coronary angiography showed no significant coronary stenosis. Due to multiple episodes of intermittent, unprovoked, high-grade AV block and ventricular standstill, she was counselled on implantation of a dual-chamber permanent pacemaker after undergoing cardiac magnetic resonance (CMR) imaging to evaluate for possible infiltrative and cardiomyopathic processes. CMR imaging showed globally increased native T1 values (1188 ms) and elevated cardiac extracellular volume (ECV) fraction (46%) without myocardial late gadolinium enhancement (LGE) in the left ventricle (Figure 4 and 5), suggesting a possible early cardiac infiltrative process.

Extensive haematological evaluation was undertaken, including evaluation of her immunoglobulin levels, which showed she had failed to respond to lenalidomide and steroid combination therapy (Table 1). She was switched to a daratumumab-based treatment regimen and discharged with fluid restriction advice, oral maintenance diuretics as well as joint cardiology-haematology clinic follow-up. Subsequent review 5 months later showed both clinical and biochemical response to daratumumab. Patient was euvolaemic and her pacemaker device interrogation revealed normalisation of AV conduction system with no pacing required from pacemaker.

Discussion

Cardiac involvement in PS is rare. Previous literature featured only case reports illustrating varied cardiac manifestations, namely pulmonary hypertension, cardiomyopathy and left ventricular systolic dysfunction with or without hypertrophy, and complete heart block.^{3–7} Many cytokines have been implicated in the pathophysiology of PS. In contrast to other plasma cell dyscrasias,

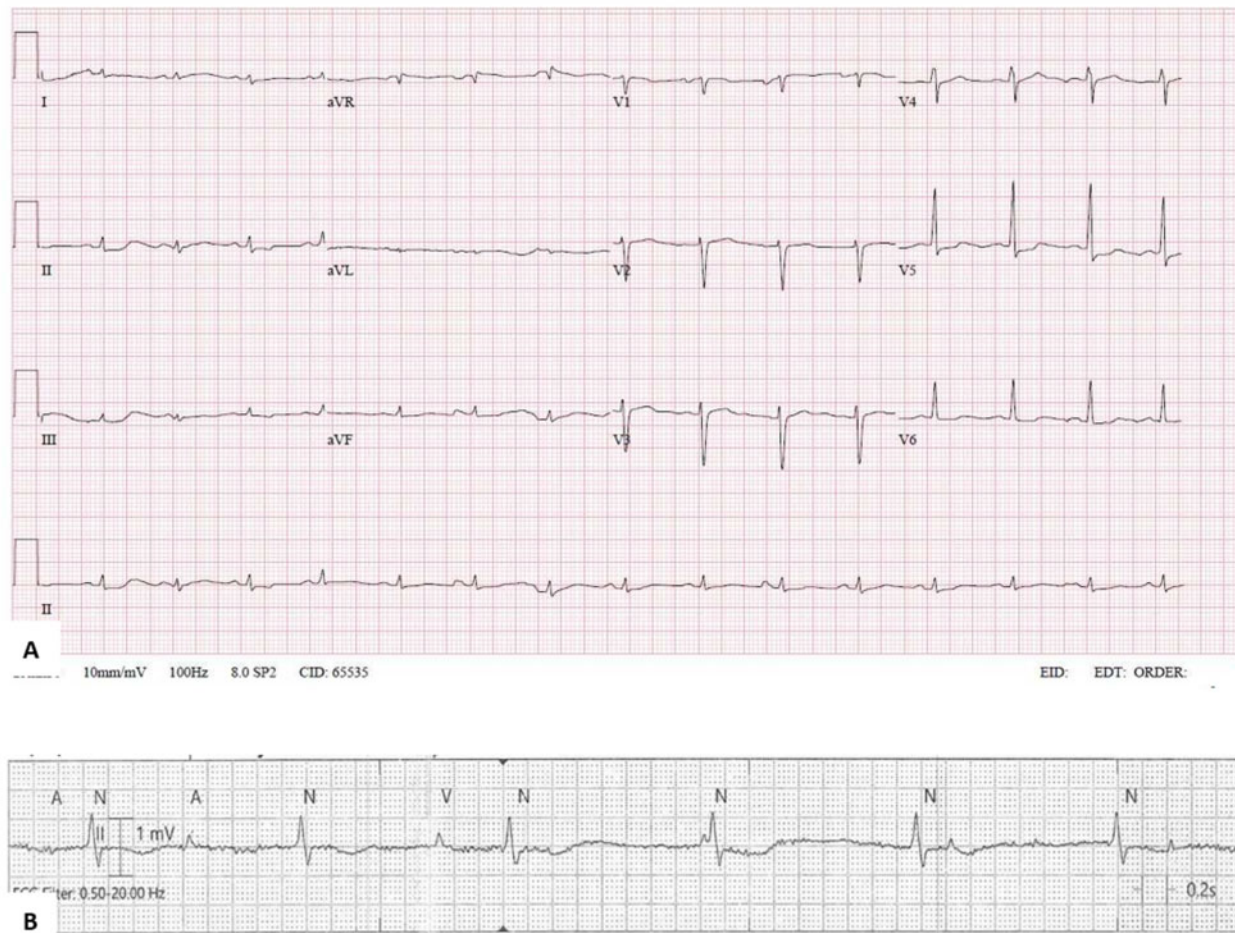


Figure 2 A 12-lead electrocardiogram demonstrating normal sinus rhythm with subtle ST depressions in the inferolateral leads and small voltages in the limb leads (A). Cardiac telemetry monitoring demonstrating complete heart block with atrioventricular dissociation and narrow QRS escape rate of approximately 38 b.p.m. (longest episode lasted for 30 min) (B).

VEGF is believed to be the key proinflammatory cytokine. It increases capillary permeability with extracellular fluid overload and additionally stimulates endothelial proliferation, activates smooth muscle cells, and induces vascular endothelial dysfunction.^{2,8–10}

Our patient with PS had cardiac involvement as evidenced by features of myocardial interstitial expansion on CMR and severe bradyarrhythmia. This may be related to VEGF overexpression leading to left ventricular oedema and myocardial ischaemia due to increased distance between the coronary arterial beds and the myocardium. Takahashi *et al.*⁴ demonstrated elevated native T1 and ECV without LGE in patients with PS-related cardiac involvement. These CMR mapping parameters improved after successful treatment for PS. Our patient had improvement in LV systolic function after aggressive diuresis with significant free water loss, further supporting ventricular oedema as a possible manifestation of cardiac involvement. Previous literature has not studied the association between improvements of LV systolic dysfunction after adequate diuresis, which may have

played a key role in the case of PS, through improvement of myocardial oedema.

Apart from fluid overload, cardiac infiltration with AL amyloid could account for the cardiac abnormalities in PS. Adami *et al.*¹¹ was one of the first to report AL amyloidosis to coexist with PS and Pei *et al.*¹² utilized CMR imaging to identify coexisting cardiac AL amyloid features in a patient with PS and cardiomyopathy. Pericardial effusion is closely associated with cardiac amyloidosis. Elevated native T1 and ECV values are pathognomonic for cardiac amyloidosis.¹³ Although LGE was not seen despite use of phase sensitive inversion recovery methods, mapping techniques, particularly ECV, are known to detect early AL amyloid even before LGE can be visualized.¹⁴

Ashrafi *et al.*⁶ identified a case of complete heart block in PS, with electrophysiological study performed to reveal infra-Hisian block, necessitating permanent pacemaker implantation. This could be the second reported case demonstrating distal conduction system disease related to progressive PS. Though requiring

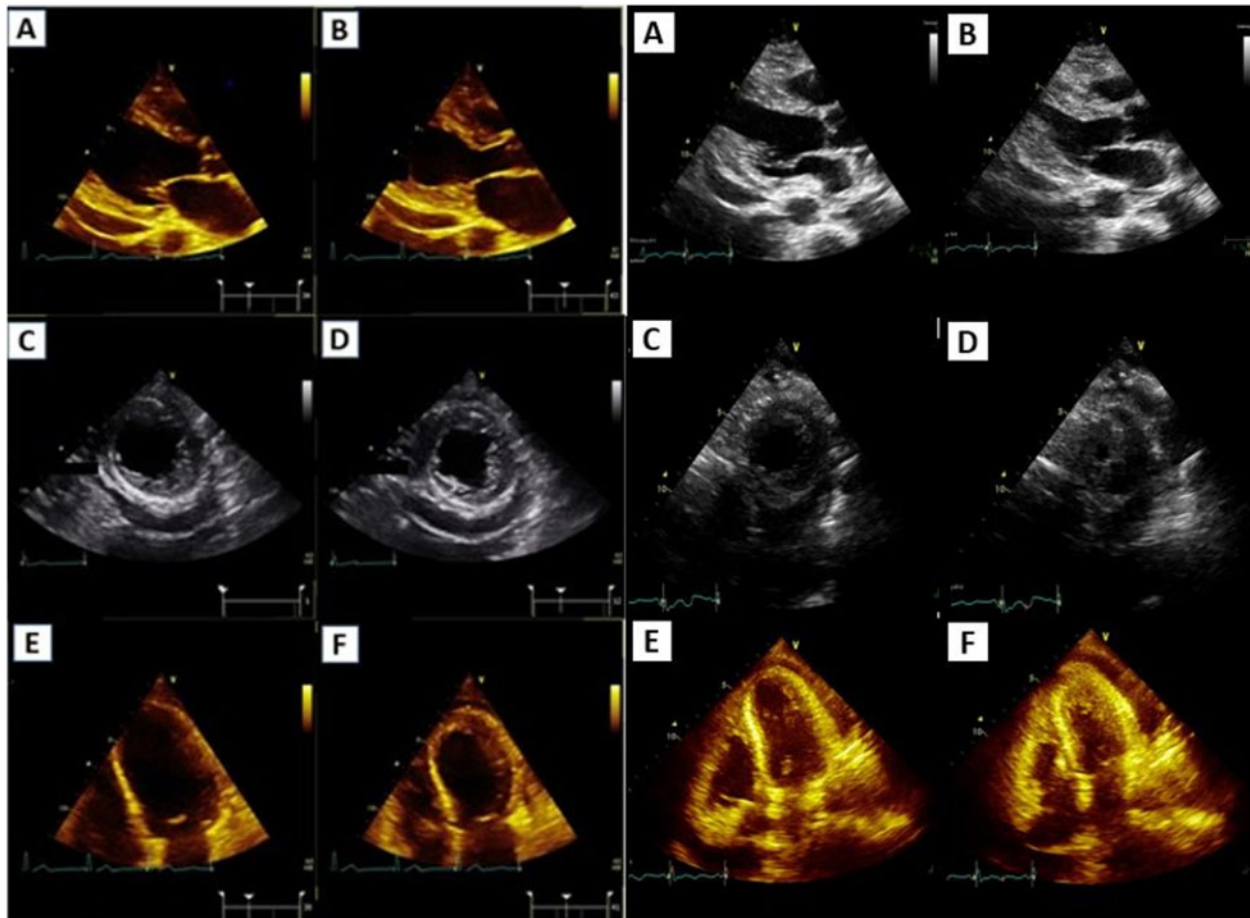


Figure 3 Transthoracic echocardiogram (*left*) demonstrating globally depressed contractility, systolic function and presence of a circumferential pericardial effusion and transthoracic echocardiogram (*right*) showing recovery in left ventricular systolic function. Echocardiographic images (A) during end-diastole and (B) end-systole of parasternal long-axis (PLAX) view, (C) during end-diastole and (D) during end-systole of parasternal short-axis view (PSAX), (E) during end-diastole and (F) during end-systole of apical four-chamber view.

further in-vitro hypothesis testing, we postulate that the conduction system abnormality could also be related to the overexpression of VEGF or underlying cardiac infiltration. With an overall median survival of 13.7 years and 6.5 years in POEMS patients presenting with fluid overload,¹⁵ she was counselled on insertion of a permanent pacemaker device to prevent syncope and sudden cardiac arrest while she was switched to a therapeutic course of daratumumab-based therapy. Initial response to the new regimen seemed to be positive based on the immunoglobulin levels (*Table 1*).

In conclusion, we describe the first case of myocardial systolic dysfunction with significant bradyarrhythmia in a patient with PS. We postulated that VEGF-induced myocardial oedema played a key role in the widespread disruption of myocardial and electrical function. Early cardiac amyloid infiltration may also play a role in PS-related cardiac manifestations. Careful rhythm monitoring and use of cardiac imaging tools can help to guide successful treatment of cardiac sequelae in this rare disease.

Lead author biography



Dr Joo Hor Tan graduated from University of Edinburgh in 2013. He obtained his MRCP (UK) in 2016. He completed his internal medicine residency training in 2019 and is currently a first year senior resident in Department of Cardiology, Tan Tock Seng Hospital.

Supplementary material

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

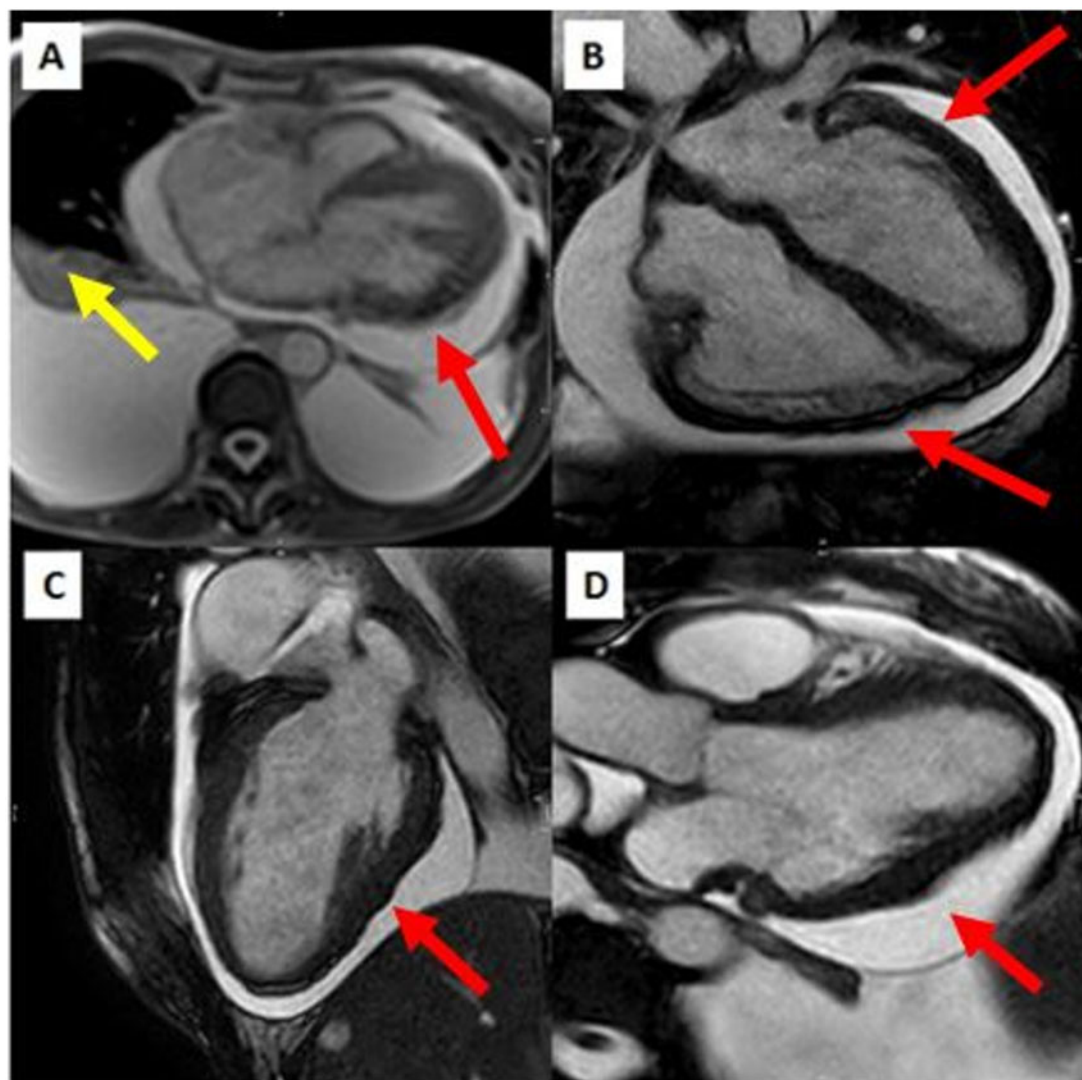


Figure 4 Cardiac magnetic resonance imaging demonstrating large bilateral pleural effusions (yellow arrow), moderate circumferential pericardial effusion (red arrows) and mildly thickened left ventricular wall in axial (A), apical four-chamber (B), apical two-chamber (C), and apical three-chamber orientations (D).

Slide sets: A fully edited slide set detailing this case 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.

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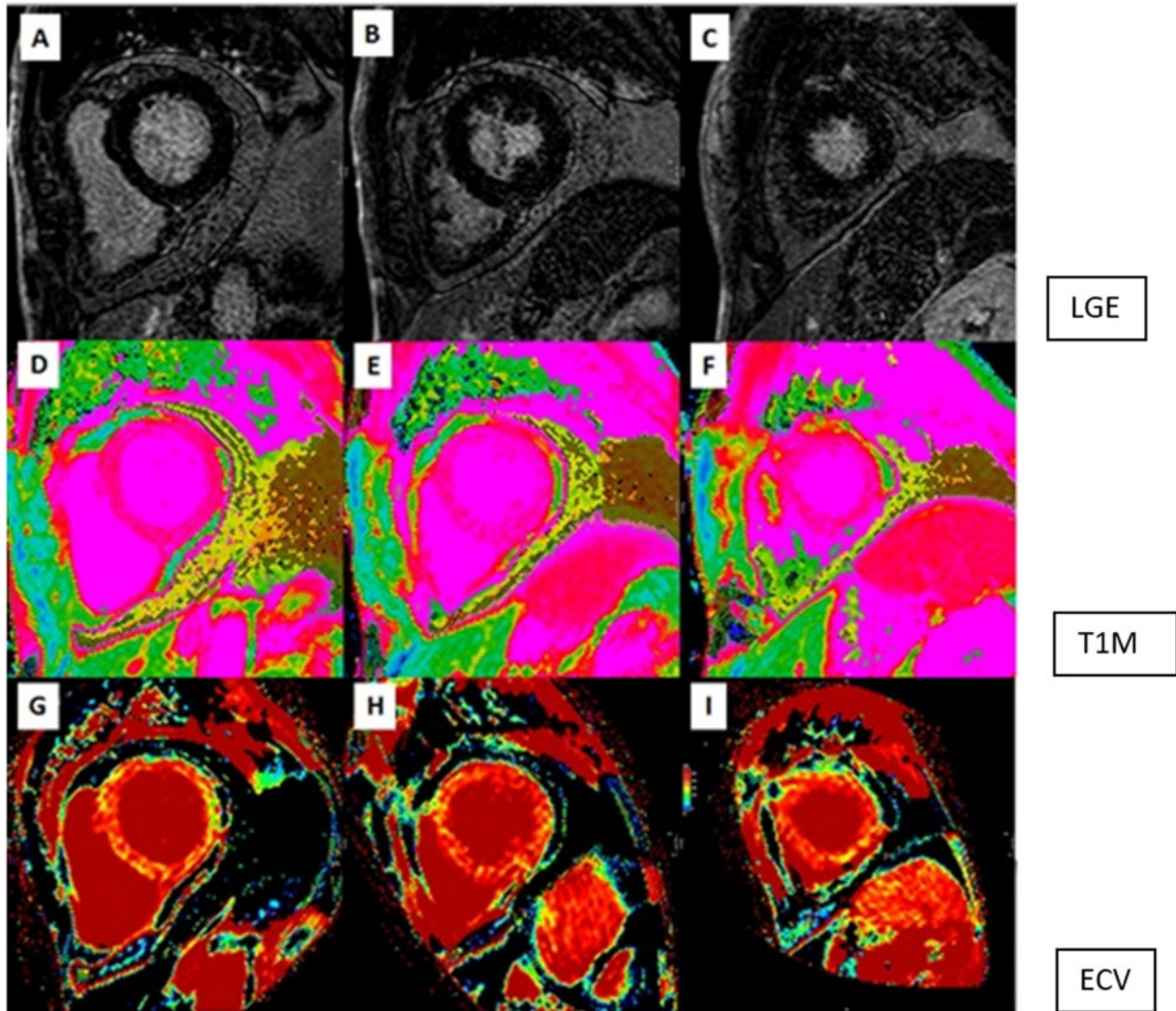


Figure 5 Representative phase sensitive inversion recovery images at basal, mid and apical left ventricular levels showing absence of late gadolinium enhancement (LGE; A–C). Both native T1 mapping (T1M; D–F) and extracellular volume quantification (ECV; G–I) also showed abnormally elevated global native T1 value (1188 ms) and ECV fraction (46%), respectively.

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