ESC European Society of Cardiology

European Heart Journal - Case Reports (2024) **8**, ytae152
https://doi.org/10.1093/ehjcr/ytae152

CASE REPORT
Heart failure

Case report: acute myocarditis complicated with persistent complete heart block: a clinical dilemma when myocardial inflammation remains

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Received 16 June 2023; revised 14 March 2024; accepted 19 March 2024; online publish-ahead-of-print 22 March 2024

Background Atrioventricular conduction abnormalities due to acute myocarditis are typically transient and do not require ventricular pacing beyond the acute phase of myocardial inflammation. Notwithstanding, selective injury and necrosis of the heart's conduction system may lead to persistent complete heart block (CHB) requiring device implantation.

Case summary We report the case of a 23-year-old man with acute lymphocytic myocarditis complicated by cardiogenic shock, cardiac arrest due to ventricular fibrillation, and persistent CHB. Endomyocardial biopsy (EMB) showed signs of subacute myocarditis, with no evidence of granulomas or giant cells, nor criteria for eosinophilic myocarditis. Aetiological work-up found serological evidence of previous Epstein–Barr virus (EBV) infection; *Borrelia burgdorferi* serology for Lyme disease was negative. The real time–polymerase chain reaction (RT–PCR) of the EMB was positive for the presence of EBV DNA, but *in situ* hybridization for viral ribosomal RNA (rRNA) was negative. The patient progressed favourably, and left ventricle ejection fraction recovered 2 weeks after initial presentation. However, CHB persisted for more than 3 weeks, and the patient underwent definitive pacemaker implantation with left bundle branch pacing.

Discussion Persistent CHB after acute myocarditis is generally considered unlikely, but in rare circumstances the damage portended by inflammation may be irreversible. Besides the play of chance, possible mechanisms behind the apparent predilection for the conduction system of the myocardium warrant further research.

Keywords Cardiogenic shock • Case report • Complete heart block • Endomyocardial biopsy • Myocardial inflammation • Myocarditis

ESC curriculum 2.2 Echocardiography • 5.9 Pacemakers • 6.4 Acute heart failure • 6.5 Cardiomyopathy • 2.3 Cardiac magnetic resonance

Learning points

- Severe acute myocarditis can have a deadly course when complicated with ventricular arrhythmias and/or cardiogenic shock.
- Acute myocarditis aetiological work-up is essential to manage its therapeutic approach.
- Complete heart block is an unusual presentation; its persistence with the need for a pacemaker is even rarer. It is essential to carefully choose the type of pacemaker to implant to minimize future desynchrony and left ventricle systolic dysfunction.

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Handling Editor: Diego Araiza-Garaygordobil
Peer-reviewers: Ana Filipa Cardoso; Diego Araiza-Garaygordobil
Compliance Editor: Elton Luo

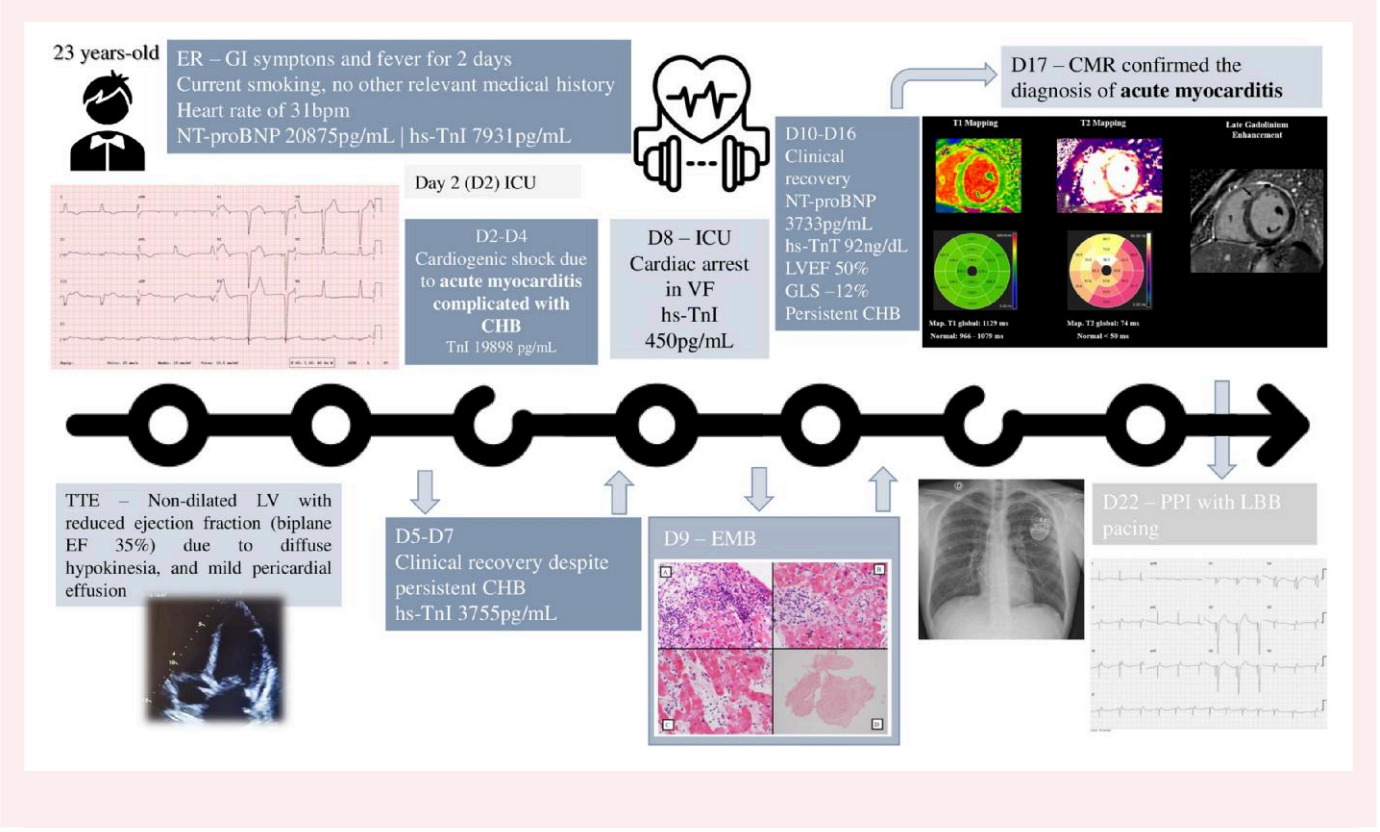
Introduction

Myocarditis is an inflammatory disease of the heart with a broad number of aetiologies.[1] Viral infections are the prevailing cause in the developed world, afflicting patients across all ages.[2] Although most presentations are mild and follow a benign clinical course, a wide variability is seen, with myocardial oedema and inflammation having the potential to compromise left ventricular (LV) systolic function, ultimately leading to acute heart failure (HF) and cardiogenic shock.[3] Significant tachy and/or bradyarrhythmias may also occur but are typically restricted to the acute phase.

No targeted treatment is advocated beyond supportive measures. Likewise, in the presence of complete heart block (CHB), it is recommended to wait for inflammation to subside, as this usually allows recovery of normal atrioventricular conduction.[4] Exceptionally, specific histologic subtypes responsive to aggressive immunosuppression may be present in fulminant cases, justifying systematic endomyocardial biopsy (EMB).[1,5,6]

We describe a case of acute fulminant myocarditis in a young patient that progressed to persistent CHB.

Summary figure



CHB, complete heart block; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; ER, emergency room; GI, gastrointestinal; GLS, global longitudinal strain; hs-TnI, high sensitivity-troponin I; ICU, intensive care unit; LBB, left bundle branch; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminus of the B-type natriuretic peptide; PPI, permanent pacemaker implantation; TTE, transthoracic echocardiogram; VF, ventricular fibrillation.

Case presentation

A 23-year-old male was admitted to the emergency room due to fever, vomiting, diarrhoea, and dizziness for the past 2 days, associated with flu-like symptoms. He denied any chest pain. He had smoking habits, occasional cannabinoids consumption, and no other history of drug abuse. He denied any previously known cardiovascular or non-cardiovascular disease or any relevant family history. He denied taking any regular medication. The physical examination was remarkable for a heart rate of 31 b.p.m. Initial work-up showed ECG in sinus rhythm and CHB with a wide QRS escape rhythm (*Figure 1A*). Laboratory findings were as follows: NT-proBNP 20 875 pg/mL, high sensitivity-troponin I (hs-TnI) 7931 pg/mL (reference range ≤ 20 pg/mL), leucocytosis, and elevated C-reactive protein. The transthoracic echocardiogram (TTE) revealed a non-dilated LV with an ejection fraction of 35% due to diffuse hypokinesia (*Figure 1B*). The diagnosis of acute myocarditis complicated with CHB was made, and the patient was admitted in the intensive care unit.

Hypotension, peripheral hypoperfusion, and global respiratory failure due to pulmonary oedema quickly ensued (*Figure 2*), requiring invasive mechanical ventilation and norepinephrine infusion. A temporary pacemaker was implanted with a pacing rate of 80 beats/min. Invasive pulse-contour analysis using Vigilelo® (Edwards) showed low cardiac output (cardiac index 2.3 L/min) with elevated systemic vascular resistance, consistent with cardiogenic shock. Blood cultures and viral nasopharyngeal swab were negative. An EMB and coronary angiography were also considered, however they were not readily available and, therefore, they were not immediately performed. Nonetheless, regarding coronary angiography, the likelihood of coronary artery disease was very low considering the typical clinical picture and the age of the

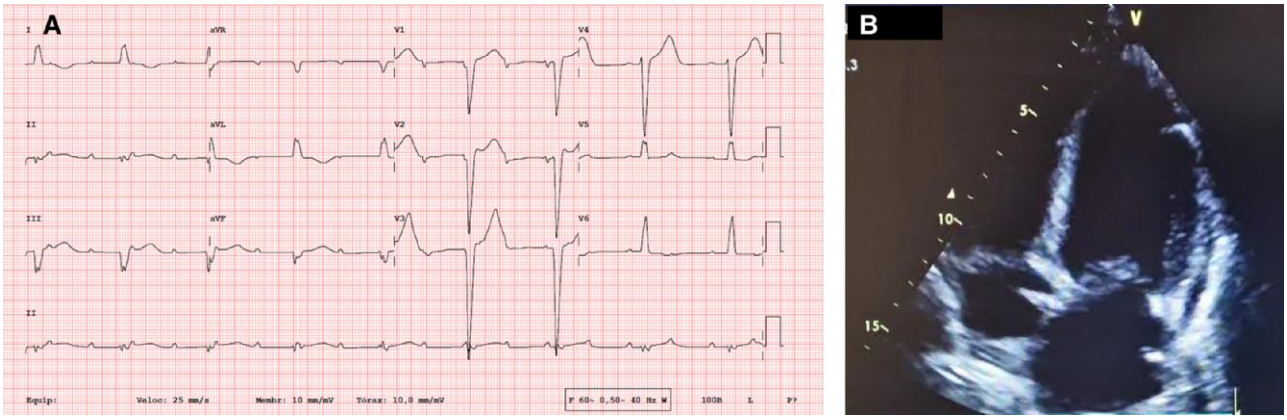


Figure 1 ECG and transthoracic echocardiogram. (*A*) ECG showing sinus rhythm, heart rate 31 b.p.m., complete heart block with a wide QRS escape rhythm. The paper speed was 25 mm/s. (*B*) Transthoracic echocardiogram showing a non-dilated left ventricle with severely reduced ejection fraction (biplane ejection fraction 35%) due to diffuse hypokinesia, normal right ventricle function and moderate functional tricuspid regurgitation with an estimated systolic pulmonary artery pressure of 64 mmHg, and a mild pericardial effusion.

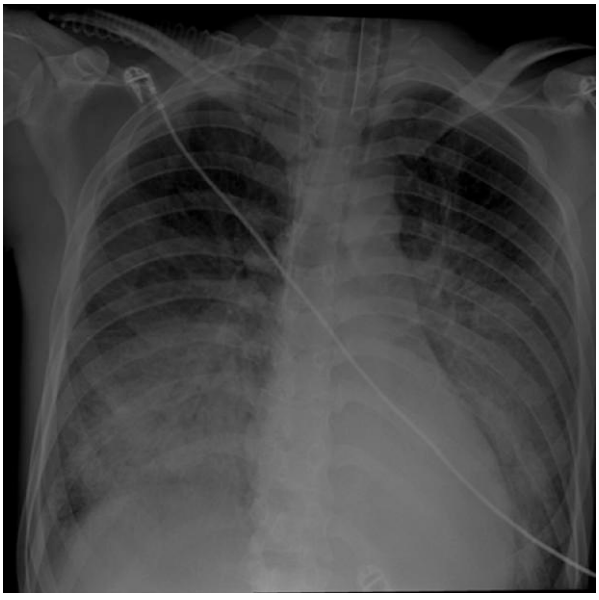


Figure 2 Thoracic X-ray. Thoracic X-ray showing bilateral pulmonary oedema.

patient. Despite the persistent CHB, a seemingly fast clinical recovery was observed, with subsequent extubation and vasopressor weaning over the next 3 days.

Seven days after the initial admission, a sudden cardiac arrest occurred, in ventricular fibrillation (VF), that was immediately defibrillated. After restoration of sinus rhythm, CHB persisted alongside with haemodynamic stability. Considering the unpredictability of clinical progression, the patient was transferred to a tertiary centre with availability of mechanical circulatory support.

An EMB obtained from the septum and LV lateral wall showed oedema and moderate inflammatory infiltrate composed of mononuclear and polymorphonuclear cells, with eosinophils. No granulomas or giant cells were found, nor criteria for eosinophilic myocarditis were met (*Figure 3A–D*). Coronary angiography was unremarkable.

Over the next days, there was sustained clinical and echocardiographic improvement, with significant recovery of LV systolic function, despite persistent but well tolerated CHB. Additionally, a steady decline of both NT-proBNP and hs-troponin was observed. As such, temporary pacing was removed.

For further aetiological clarification and prognostication, a cardiac magnetic resonance (CMR) was performed (*Figure 4*), depicting subacute myocarditis with signs of myocardial oedema—increased native T1 and T2 in all segments, more expressive in the septal and anterior segments, with diffuse mid-wall late gadolinium enhancement (LGE). Viral serology was consistent with previous Epstein–Barr virus (EBV) infection, with negative serology for Lyme disease and human immunodeficiency virus (HIV) infection. The real time–polymerase chain reaction (RT–PCR) of the EMB was positive for EBV DNA, but *in situ* hybridization for ribosomal RNA (rRNA) was negative. Taken together, these findings were highly suggestive of lymphocytic myocarditis. Despite the presence of septal myocardial oedema, a multidisciplinary decision to not initiate immunosuppressive therapy was made on the grounds of EBV re-activation risk and absence of a histological responsive phenotype.

After discussion, the patient underwent permanent pacemaker implantation (PPI) (DDD) with left bundle branch pacing after 3 weeks of unremitting CHB (*Figure 5*). Considering the rapid and spontaneous LV function recovery (within 15 days), the patient was only discharged with an angiotensin-converting-enzyme inhibitor. Mineralocorticoid receptors antagonists and sodium-glucose transport protein 2 inhibitors were never initiated considering the rapid clinical course and fast LV function recovery. Six months later, he remained asymptomatic, with a stable escape rhythm of 40–45 beats/min, well tolerated at rest or during mild activities, albeit with chronotropic incompetence for more demanding physical efforts, during which 100% ventricular pacing is required. Unfortunately, he refused to repeat CMR at 3 months to re-evaluate LGE extension and LVEF.

Discussion

This case is noteworthy for an unexpected persistent CHB after acute myocarditis complicated by cardiogenic shock and VF. Bradyarrhythmias

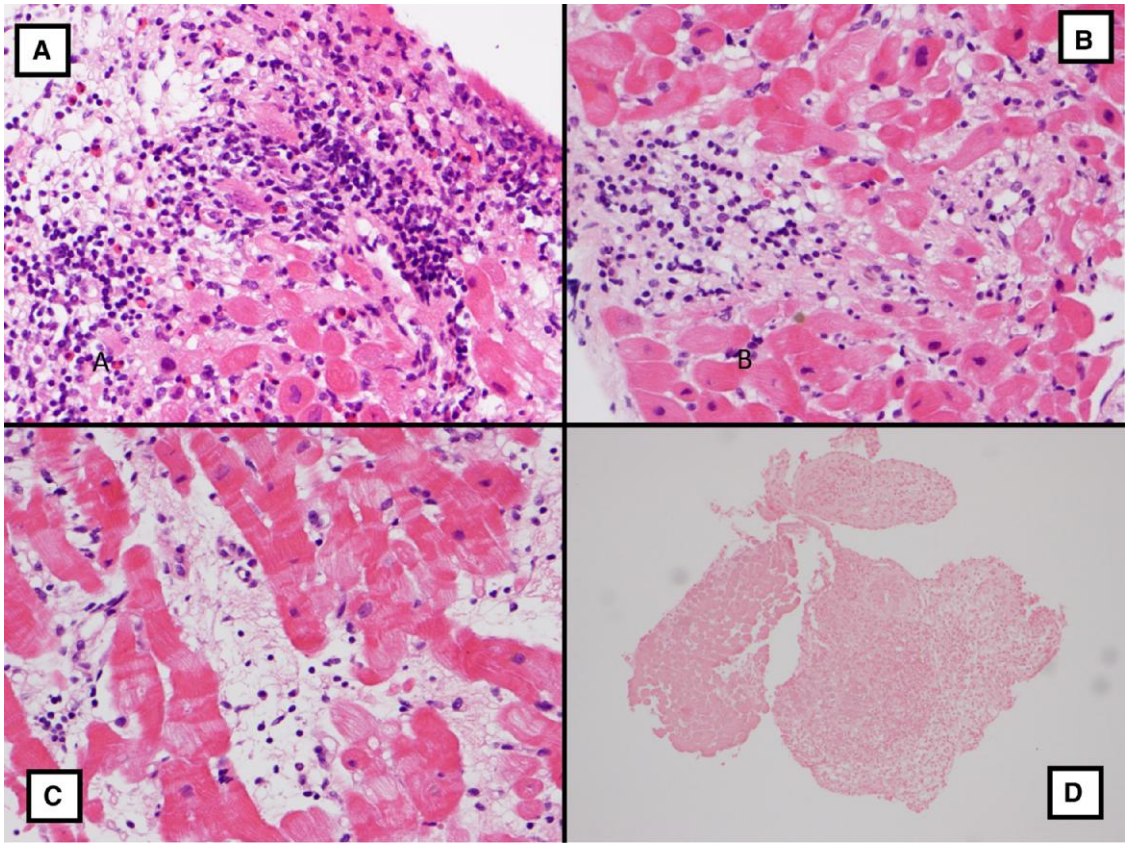


Figure 3 Endomyocardial biopsy. (*A*,*B*) HE. Mixed inflammatory infiltrate (mononuclear and polymorphonuclear cells with eosinophils). (*C*) HE. Oedema. (*D*) CISH. *In situ* hybridization negative for Epstein–Barr virus. CISH, chromogenic *in situ* hybridization; HE, haematoxylin–eosin dye.

are a rare and mostly transient manifestation in the setting of acute myocarditis, appearing mainly in children and seldomly in adults,[7] with reported rates of atrioventricular blocks ranging from 0.8 to 1.7–10%.[4] Persisting arrhythmias beyond the acute phase (>1 week) suggest myocardial fibrosis and chronic inflammation, anticipating a low likelihood of recovery.[8]

In our patient, the CMR findings of extensive anteroseptal fibrosis provided the pathophysiological basis for CHB persistence. Presence of LGE, particularly in the mid-layer LV septal segment, is common in patients with HF or arrhythmias. Also, the maintenance of CHB despite normalization of cardiac biomarkers, surrogates of myocardial inflammation, concurred to the low probability of native atrioventricular conduction recovery. Despite being well tolerated, the foreseeable and later confirmed chronotropic incompetence made the decision to proceed to PPI inevitable. Since LV function had normalized, left bundle branch pacing was preferred over cardiac resynchronization therapy (CRT), mimicking physiological auriculoventricular conduction and reducing the risk of subsequent desynchrony induced LV dysfunction. The timing to PPI was decided considering the timeline of the events: presence of persistent CHB beyond 2 weeks after the initial presentation, absence of active signs of inflammation at 3 weeks (i.e. normal cardiac biomarkers and LV function recovery) and the evidence of irreversible damage on CMR. These findings supported the 3 weeks timespan to PPI.

Late onset VF highlights the unpredictable nature of myocarditis. Severe cases often exhibit cardiac arrhythmias, mostly in non-lymphocytic (giant cell myocarditis and cardiac sarcoidosis-related myocarditis) or HIV-related myocarditis, especially in the acute phase.[4] The mechanisms underlying arrhythmogenesis in myocardial inflammation are poorly understood.[4] Furthermore, predicting progression from myocarditis to scar formation varies greatly, complicating clinical decision-making.[9] The medical team decided not to proceed to implantable cardioverter-defibrillator (ICD) implantation considering that right ventricle pacing (highly likely considering the irreversible nature of the CHB previously discussed) might exacerbate/cause LV dysfunction, potentially leading to the need to CRT-D upgrade in the future. To mitigate these complications associated with ICD and considering the acute nature of the VF in the context of significant myocardial oedema and active inflammation (and not fibrosis *per se*), the choice was to implant left bundle branch pacing exclusively. This approach is more physiological and carries a significantly lower risk of cardiac desynchronization.

The sensitivity of RT–PCR in detecting viral genomes in EMB is uncertain.[2] Molecular tests including *in situ* hybridization and EBV RT–PCR are more sensitive than serological assays, which can't differentiate primary infection from re-activation.[10] *In situ* hybridization detects active viral replication through EBV rRNA.[11] The presence of EBV DNA in our patient may indicate latent infection. Moreover, serum EBV viral load was undetectable. Even so, despite the low probability of EBV-induced myocarditis, the overall clinical picture was highly suggestive of acute lymphocytic myocarditis—previous history of respiratory infection, no evidence of giant cell nor non-caseous granulomas on EMB, and negative serology for Lyme disease and HIV. Although viral infection remains the most likely first cause of lymphocytic myocarditis in clinical practice, PCR analyses are negative in most cases.[12] Current evidence does not support the use of immunosuppression in such

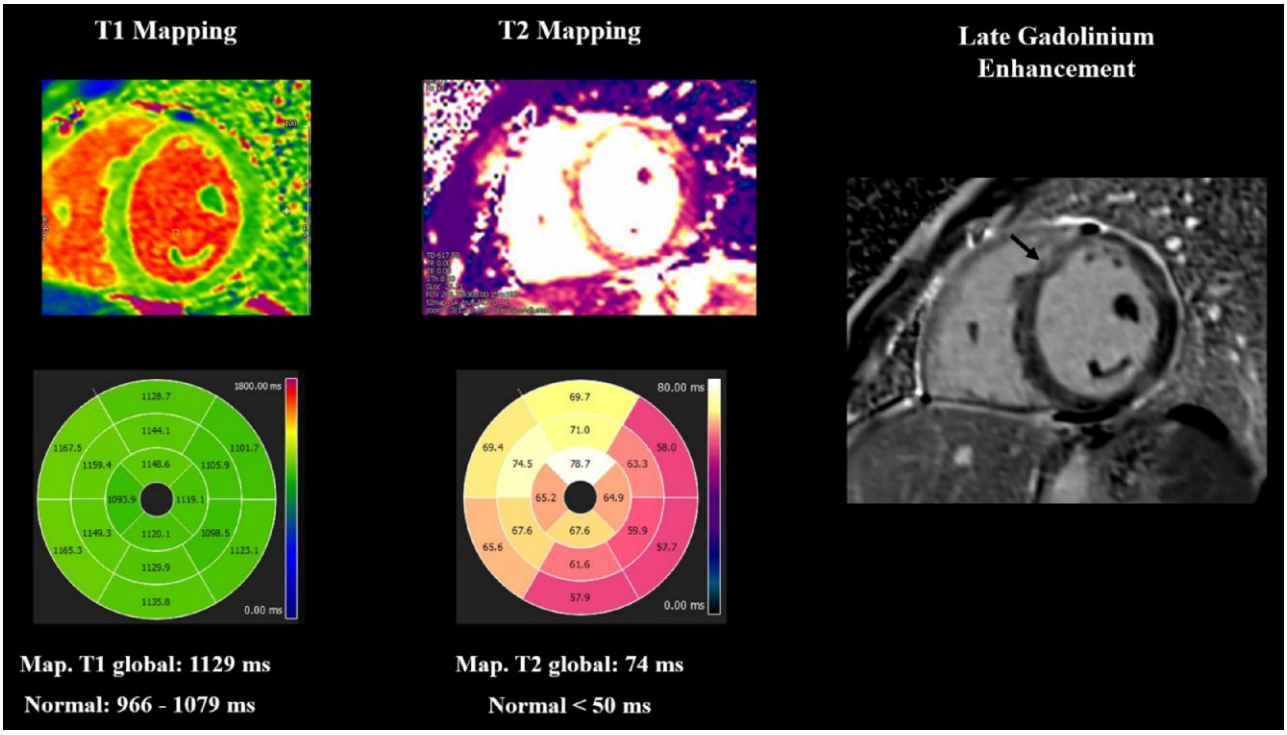


Figure 4 Cardiac magnetic resonance. Subacute myocarditis with signs of myocardial oedema/active inflammatory process (increased native T1 and T2 increased in all segments, more expressive in the septal and anterior segments). Slight biventricular dilation (index left ventricular end-diastolic volume 118 mL/m^2) with borderline left ventricle function (54%) and a preserved right ventricle ejection fraction (58%). Signs of circumferential pericardial inflammation, without effusion. Black arrow: area of late gadolinium enhancement.

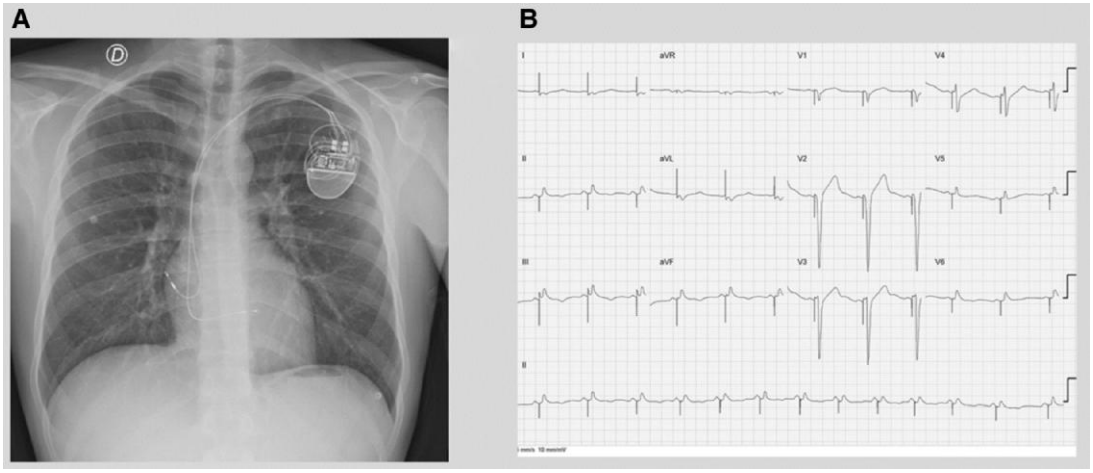


Figure 5 Final result. (*A*) Definitive pacemaker implantation with left bundle branch pacing. (*B*) ECG in sinus rhythm with ventricular pacing and narrow QRS complex. The paper speed was 25 mm/s.

cases,[2,4] especially in the absence of sufficient clinical evidence of autoimmune/auto-inflammatory aetiologies, which, together with the CMR findings, weighted unfavourably to the decision to initiate it. Additionally, the use of empirical antiviral therapy in acute lymphocytic myocarditis did not improve outcomes, and it is not currently recommended.[12] There are no recommendations regarding its use in the absence of specific biopsy-proven viral myocarditis, such as CMV, HIV, or HHV6. Therefore, we did not consider that its use was indicated.

Jiang et al.[13] previously reported the case of a fulminant myocarditis complicated with recurrent arrhythmias with haemodynamic instability, where temporary His bundle pacing was essential for patient's clinical recovery. However, and to the best of our knowledge, this is the first reported case of myocarditis complicated by cardiogenic shock, VF, and persistent CHB requiring left bundle branch pacing. Besides the play of chance, mechanistic insights behind the consequences of a specific and possibly rare individual virus–host interaction on the conduction system of the myocardium warrant future research.

Lead author biography

Maria Rita Lima received her Master's degree in Medicine from the Faculty of Medicine, University of Lisbon in 2019. She is currently a cardiology intern at Santa Cruz Hospital, Lisbon, Portugal. She has previously published a review article regarding septic cardiomyopathy. Her current focus is on the pathophysiology of heart failure and its management. She also has a special interest in acute cardiac care field.

Acknowledgements

The authors would like to express their gratitude to all colleagues who cooperate in providing data for the current analysis.

Consent: The authors have obtained consent from the patient to publish this case report, including images, in accordance with COPE guidelines.

Conflict of interest: None declared.

Funding: The present study was a local centre investigation, without any funding by external entities.

Data availability

All data exposed in this case report were acquired from our institution, after obtaining informed consent from the patient.

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