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CASE REPORT
Cardiac imaging

Case report of isolated cardiac sarcoidosis presenting as hypertrophic obstructive cardiomyopathy—a clinical picture printed on lenticular paper

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Background Cardiac sarcoidosis (CS) is an inflammatory granulomatous process of the myocardium that can be asymptomatic or have several different clinical phenotypes. One of its rarely described presentations consists of hypertrophy of the septal myocardium, similar to hypertrophic cardiomyopathy (HCM). Isolated cardiac sarcoidosis that haemodynamically mimics hypertrophic obstructive cardiomyopathy (HOCM) has been rarely described in the literature.

Case summary A 64-year-old Caucasian female previously diagnosed with non-critical aortic stenosis presented with pre-syncope, and echocardiography showed significant obstruction based on left ventricular outflow tract gradients, confirmed by cardiac magnetic resonance (CMR), concerning for a phenocopy of HCM. Septal myectomy was performed and pathology specimen revealed non-caseating granulomata consistent with cardiac sarcoidosis. She was started on oral corticosteroids and initial cardiac fluorodeoxyglucose positron emission tomography (FDG-PET) done after 1 month of treatment was negative. Repeat FDG-PET 15 months later, in the setting of haemodynamic decompensation, demonstrated diffuse FDG uptake in the myocardium without extra-cardiac involvement.

Discussion Our case brings together two entities: isolated cardiac sarcoidosis and its presentation mimicking HOCM, which has been very rarely described in the literature. And it also shows the scenario of surgical pathology diagnosis of sarcoidosis that was not suspected by initial CMR or FDG-PET, despite adequate preparation, only appearing on repeat FDG-PET done 15 months later. Isolated cardiac sarcoidosis should remain a differential diagnosis for any non-ischaemic cardiomyopathy without a clear cause, despite imaging evidence of HCM.

Keywords Case report • Isolated cardiac sarcoidosis • Hypertrophic obstructive cardiomyopathy • Septal myectomy • Cardiac magnetic resonance imaging • Fluorodeoxyglucose positron emission tomography

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Learning points:

- Cardiac saroidosis is a possible differential diagnosis for hypertrophic obstructive cardiomyopathy
- Cardiac sarcoidosis may present even in the absence of extra-cardiac disease and should be in the differential diagnosis of non-ischemic cardiomyopathies.
- Demonstration of non-caseating granulomata on biopsy (cardiac or extra-cardiac) is an important step in the diagnostic evaluation of cardiac sarcoidosis.

Introduction

Cardiac sarcoidosis (CS) is an inflammatory granulomatous process of the myocardium with a relatively broad range of clinical presentations, from asymptomatic to decompensated heart failure, malignant arrhythmias, and sudden cardiac death (SCD).[1] Cardiac sarcoidosis with overt symptoms is usually present in less than 5% of the patients with sarcoidosis, but studies using cardiac magnetic resonance (CMR) in asymptomatic patients with diagnosed sarcoidosis showed cardiac involvement to be as high as 30%.[2,3] Cardiac sarcoidosis can also present with several different imaging phenotypes, including left ventricular (LV) dilatation, regional wall motion abnormalities with either focal aneurysmal or regional wall thickening, valvular dysfunction, and pericardial effusions.[4–6] Another one of its several possible presentations consists of asymmetric hypertrophy of the septal myocardium,[7,8] but systolic anterior motion (SAM) and dynamic left ventricular outflow tract (LVOT) obstruction have been rarely described previously.

Timeline

At presentation	Patient presented with pre-syncope. Echocardiogram and cardiac magnetic resonance imaging suggestive of hypertrophic cardiomyopathy with left ventricular outflow tract obstruction
7 months after presentation	- Cox Cryo Maze IV procedure and septal myectomy performed. - Myectomy histopathology showed non-caseating granulomata.
10 months after presentation	- Started on Prednisone
11 months after presentation	- Cardiac and whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) negative
2 years after the presentation	Admitted with decompensated heart failure. Repeat cardiac and whole-body FDG-PET showing diffuse myocardial FDG uptake without perfusion defects. No extra-cardiac FDG uptake. Patient initiated on Methotrexate and planned Prednisone taper.

Case presentation

A 64-year-old Caucasian female presented with dizziness, pre-syncope, and progressive decline in functional capacity, with New York Heart Association (NYHA) class III symptoms. Her past medical history was significant for atrial fibrillation, type II diabetes mellitus, hypertension, hyperlipidaemia, prior tobacco use, chronic obstructive pulmonary disease, and idiopathic thrombocytopenia. She also had been previously diagnosed with aortic stenosis, which prompted admission for further evaluation of progression. Family history was significant for coronary artery disease in her parents and brother, and colon cancer in the mother. Physical exam was significant for a holosystolic murmur radiating to the axilla, and bilateral lower extremity oedema, otherwise unremarkable. Initial electrocardiogram (ECG) showed normal sinus rhythm without LV hypertrophy or significant ST/T wave abnormalities (*Figure 1*). Echocardiography showed normal LV systolic function, Grade II LV diastolic dysfunction, and moderate septal LV hypertrophy (1.7 cm at the level of mitral leaflet tips) (*Figure 2*, *Videos 1* and *2*). At rest, there was mitral valve SAM with near septal contact and a peak LVOT gradient of 48 mmHg, with resultant moderate, posteriorly directed mitral regurgitation, which increased to SAM with septal contact after provocation with Valsalva manoeuvre, showing an increase in the peak LVOT gradient to 82 mmHg (*Figure 3*). She underwent CMR imaging, which showed again septal hypertrophy, mitral valve SAM with moderately severe mitral regurgitation, and flow acceleration in the LVOT, suggestive of a haemodynamically significant obstruction (*Video 3* and Supplementary material online, *Video S1*). Interestingly, the septal thickness was less prominent by CMR (1.5 cm in the mid-inferoseptum), likely due to the inclusion of right ventricular septal trabeculation on echo and resultant overestimation of septal thickness. Cardiac magnetic resonance also defined abnormal chordal attachments from the posterior medial papillary muscle to the base of the anterior mitral valve leaflet, which were also likely contributing to LVOT obstruction (*Figure 4*). Mild delayed gadolinium enhancement was noted within the mid-myocardium of the thickened anteroseptum, as well as at the inferior right ventricle insertion point into the inter-ventricular septum (*Figure 5*). This constellation of imaging findings was most likely consistent with hypertrophic obstructive cardiomyopathy (HOCM). Surgery was indicated because of the haemodynamically significant LVOT obstruction in the setting of her NYHA Class III symptoms despite optimal beta-blocker therapy, in line with current guideline recommendations.

Because of her relatively thin upper septum and the abnormal chordal attachments seen on imaging, and also possible need for mitral valve repair, septal myectomy was favoured instead of alcohol ablation. She underwent septal myectomy with left-sided Cox–MAZE IV procedure, with left atrial appendage ligation, and intraoperative findings were consistent with concentric left ventricular hypertrophy. Despite her multimodality imaging findings being consistent with HOCM, histopathology of the myectomy did not show the classic histopathology of hypertrophic cardiomyopathy. Instead, it showed non-caseating granulomatous myocarditis (*Figure 5*) (*Figure 6*). Therefore, she was initiated on prednisone and referred for ICD implantation.

A month later, cardiac and whole-body FDG-PET were performed, with adequate preparation, and showed no FDG avid

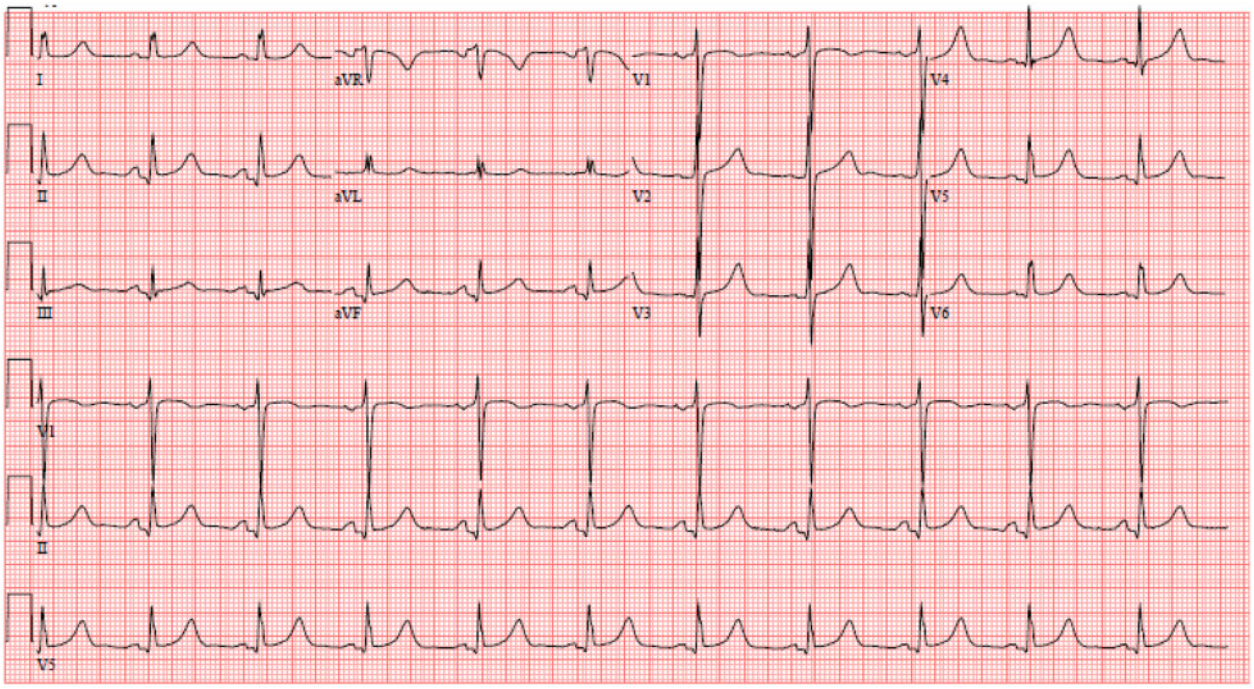

Figure 1 Electrocardiogram. Normal sinus rhythm without significant Left Ventricular Hypertrophy (LVH) and ST/T changes typical of hypertrophic obstructive cardiomyopathy.

process except for left lower lobe ground-glass opacification with minimal uptake, not typical for pulmonary sarcoidosis. A year and a half after the myectomy, during admission for decompensated heart failure, work-up with repeat echocardiogram showed mildly decreased LV systolic function and moderate mitral regurgitation, and N-terminal pro-B-type natriuretic peptide of 2175 pg/mL. Repeat cardiac FDG-PET was done, at this time showing a diffuse myocardial FDG uptake despite a good diet preparation, suggestive of active inflammation (large, more than five segments of inflamed myocardium), with no perfusion defects. Repeat whole-body PET showed no abnormal FDG avid processes in the remainder of the body, and ophthalmologic evaluation also ruled out eye involvement, suggesting a diagnosis of isolated cardiac sarcoidosis (CS). She was initiated on methotrexate with a plan to progressively taper corticosteroids.

Discussion

This case outlines isolated CS as a precise mimicker of HOCM, evident symptomatically and on multimodal imaging. It also shows surgical pathology diagnosis of sarcoidosis that was not demonstrated by initial CMR or FDG-PET. In rare circumstances, CS can precisely mimic the haemodynamics of HOCM, with systolic anterior motion (SAM) and dynamic LVOT obstruction translated into high trans-aortic pressure gradients. This specific presentation has been rarely reported previously,[9,10] and, at most occasions, patients also demonstrated biopsy-proven extra-cardiac involvement. The diagnosis of CS becomes more challenging in the setting of isolated disease, given the often absent suspicion at initial presentation, exemplified by our patient, a Caucasian female with an apparently clear picture of HOCM on two imaging modalities (echo and CMR). In the presence of known sarcoidosis, cardiomyopathy with asymmetric septal thickening by itself can prompt further investigation for CS.[11,12]

There are two main scenarios by which CS presents. One is apparent extra-cardiac sarcoidosis, where the presence of typical electrocardiographic, echocardiographic, PET, or CMR changes suffices to suspect cardiac involvement. The other is clinically isolated CS, which given the non-specificity of imaging findings becomes a difficult differential in clinical practice. This multitude of possible clinical pictures makes CS a frequently late or missed diagnosis. The constant evolution of multimodal imaging is changing the paradigm of CS, improving its diagnostic yield and becoming the standard of care for its diagnosis.[11]

Nonetheless, established diagnostic criteria for CS are neither sensitive nor specific for the detection of isolated CS, and the true prevalence of the disease confined to the heart is not known, varying depending on the diagnostic method and presentation.[13] Recent advances in the imaging field have increased diagnostic sensitivity and specificity, namely with late-gadolinium enhancement (LGE) CMR and cardiac FDG-PET, and both are now part of the diagnostic algorithm.[1,11] Late-gadolinium enhancement has been described as an imaging marker that suggests the possibility of myocardial fibrosis while cardiac PET may be more useful in the detection of the active inflammation.[11] The main issue is that there are no specific LGE patterns to identify sarcoidosis via CMR, although it is most often patchy and multifocal, located to the mid-myocardium or sub-epicardium, with a predilection for basal septum and lateral walls, in a non-coronary distribution,[8,13] so it is hard to attribute findings to CS

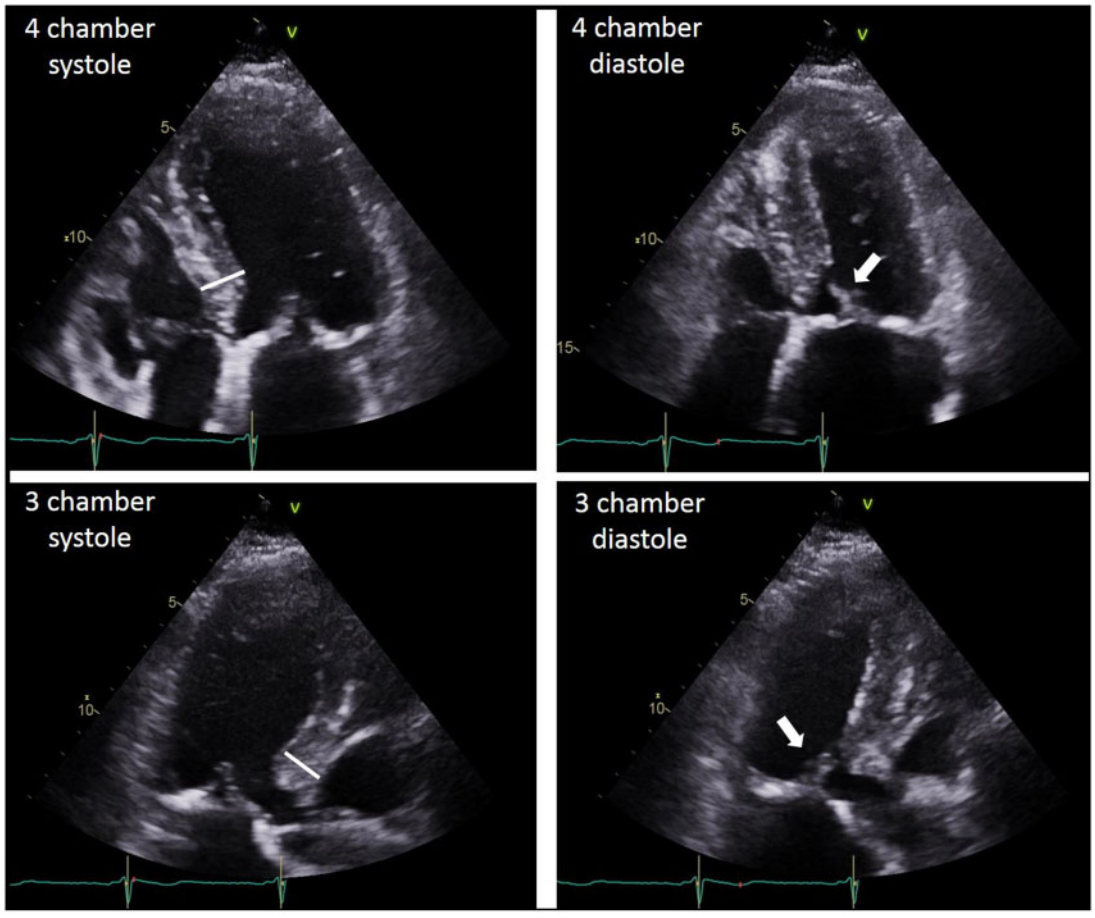

Figure 2 Echocardiography. Four-chamber and three-chamber views show moderate basal septal hypertrophy (white line) and mitral valve systolic anterior motion into the left ventricular outflow tract (white arrow).

when another cardiomyopathy appears more likely, as in our case. Our patient did not undergo cardiac FDG-PET until after histopathologic diagnosis.

Combining multimodal imaging with biopsy could also be promising. Although identifying non-caseating granulomas in cardiac tissue samples is very specific for sarcoidosis, endomyocardial biopsy has poor sensitivity, likely due to the patchy nature of the granulomas throughout the myocardium. An autopsy study of patients with cardiac sarcoidosis presenting with sudden cardiac death found the likelihood of positive biopsy findings to be about 50%, although this could be attributed to disease severe enough to present with SCD, instead of solely sarcoid cardiomyopathy.[8,14,15] It was also estimated that only one-third of the patients would have a positive ventricular septal biopsy, suggesting a potential role of cardiac imaging to guide the highest yield biopsy site and improve its sensitivity.[16]

Conclusion

To our knowledge, this is the first described case of isolated cardiac sarcoidosis presenting with anatomical and haemodynamic features mimicking HOCM. This highlights the importance of careful, multimodality evaluation to exclude alternative or concomitant pathologies, including hypertension or other infiltrative processes when evaluating these patients presenting with increased wall thickness and obstructive physiology. Salient clues such as increased LV volumes, absence of family history or relatively normal 12-lead ECG may also suggest an alternative diagnosis to HOCM, as seen in this case. Differentiation between the various causes for increased LV wall thickness and LVOT obstruction is now increasingly important with the advent of more tailored, condition-specific pharmacotherapies prior to consideration of myectomy. Therapies such as mavacamten[17] for HOCM, tafamidis and others for amyloidosis and evolving steroid-sparing strategies for sarcoidosis now provide alternative and effective therapeutic options. Hence, recognition of alternative or concurrent diagnoses masquerading as HOCM now becomes even more critical and will likely result in better prospective understanding of the pathologies contributing to this patient phenotype moving forward.

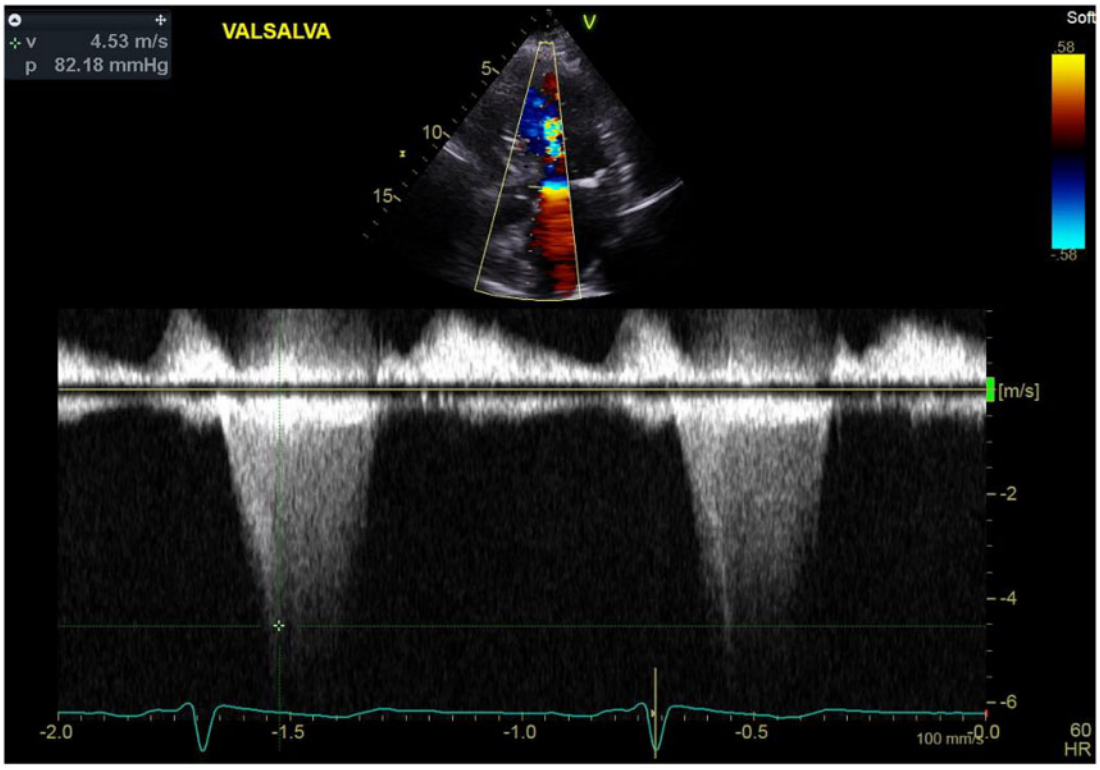

Figure 3 Echocardiography. Continuous wave spectral Doppler demonstrating a peak gradient through the left ventricular outflow tract of approximately 82 mmHg with Valsalva manoeuvre in the context of mitral valve systolic anterior motion (SAM).

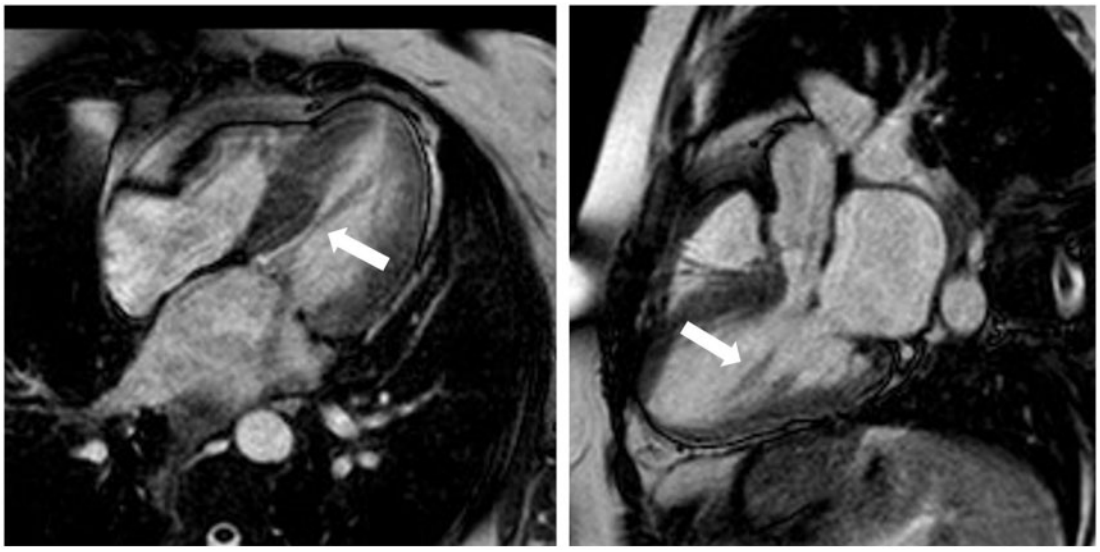

Figure 4 Cardiac magnetic resonance imaging. Steady state free precession sequences showing abnormal papillary muscles with multiple accessory bundles and abnormal chordal attachments on four-chamber (left image) and three-chamber (right image) views.

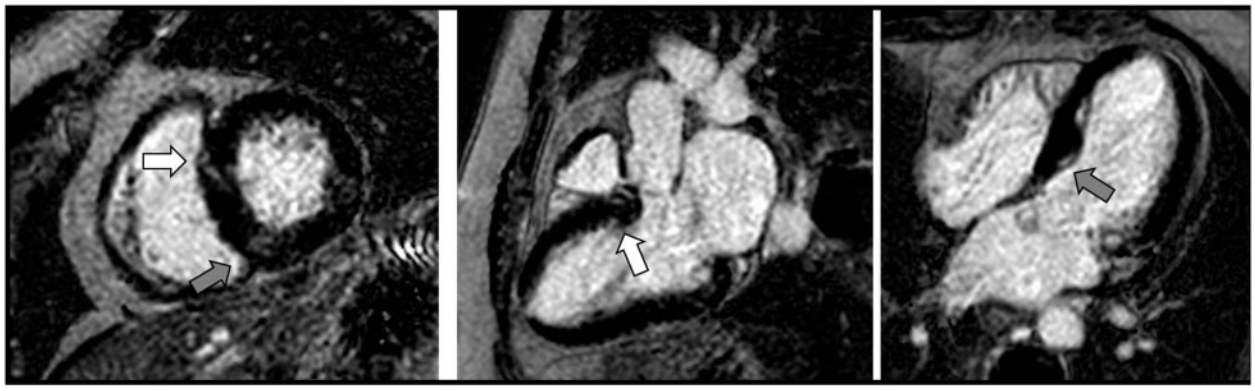

Figure 5 Cardiac magnetic resonance imaging. Delayed gadolinium enhancement imaging of the left ventricle from basal short axis, three-chamber (left ventricular outflow tract) and four-chamber views. Mild, patchy, mid-myocardial delayed enhancement is demonstrated in the anterior (white arrows) and inferior (grey arrows) segments of the basal inter-ventricular septum.

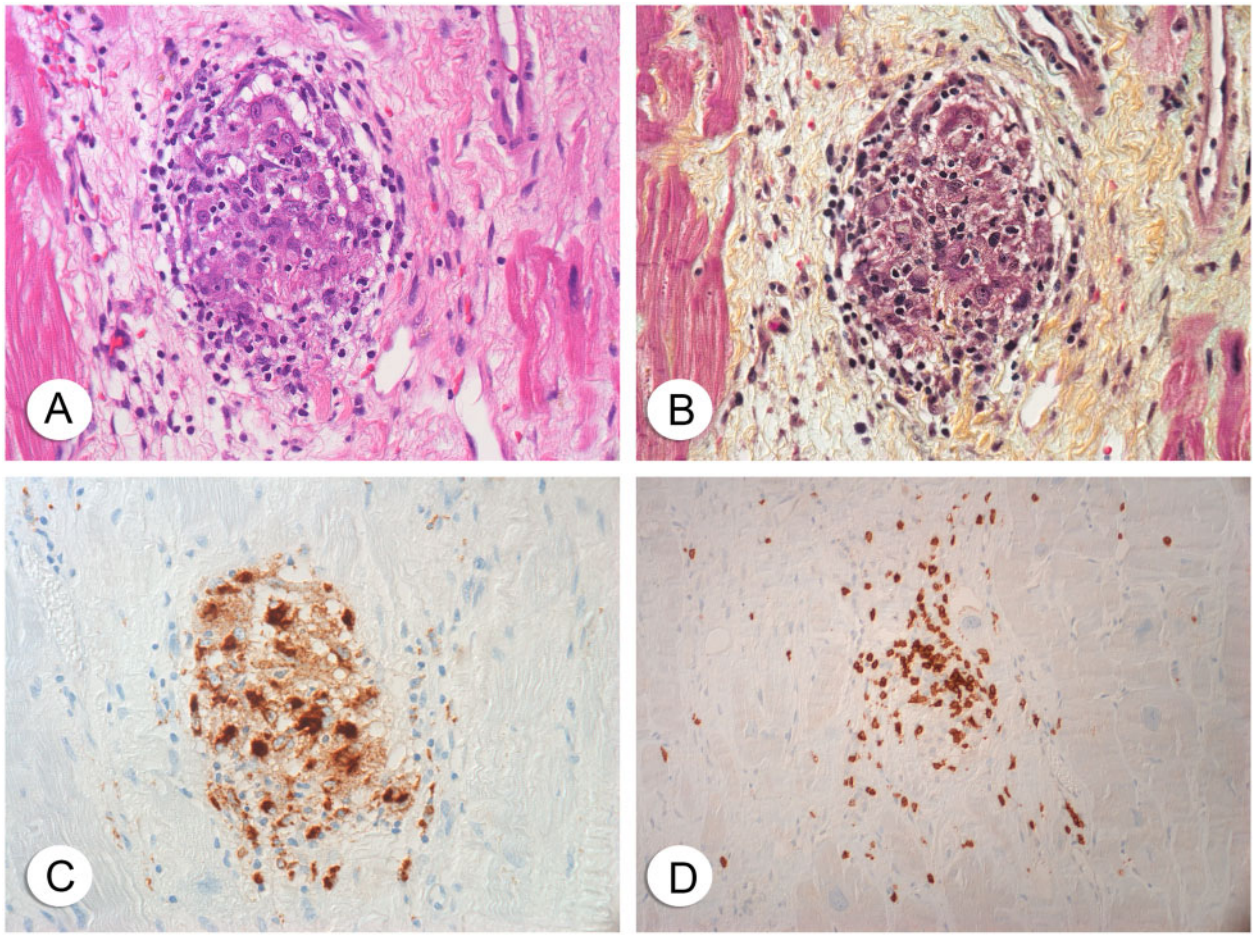

Figure 6. Non-caseating granulomatous myocarditis. (*A*) Light microscopy shows multiple areas of granulomata formation with accompanying early fibrosis. Note the absence of myocyte disarray. There is no small intramural coronary artery dysplasia. Instead, there are granulomata with histiocytes, lymphocytes and early formation of multinucleated giant cells. Many of these were present throughout the sample. None of the granulomata showed caseating necrosis. Stains for microorganisms (not shown) were negative. (H&E, ×400) (*B*). A Movat pentachrome stain shows the same granuloma seen in (*A*). The yellow connective tissue surrounding the granuloma is early fibrosis (loose connective tissue) (Movat, ×400). (*C*) Immunohistochemistry for CD68 shows the macrophages and giant cell staining brown (positive) (CD68, ×400). (*D*) CD3 staining shows lymphocytes present in the granuloma (CD3, ×400).

Lead author biography

Dr Isadora Sande Mathias is a physician graduated from Universidade Federal da Bahia, in Salvador, Brazil, in 2017, and is currently completing internal medicine training at the Cleveland Clinic Foundation, in Ohio, United States, prospectively initiating Cardiology fellowship in 2021 at the Houston Methodist Hospital.

Supplementary material

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

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

Consent: The patient described in this case report has subsequently passed away. The Institutional Review Board of Cleveland Clinic stated that approval was not required for a case report of a single patient. This was discussed with the editors.

Conflict of interest: None declared.

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