Fulminant cardiac sarcoidosis resembling giant cell myocarditis: a case report

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Background
Severe cardiac sarcoidosis (CS) can share clinical and histopathologic features with giant cell myocarditis (GCM).

Case summary
A 56-year-old female presented with 1 week of exertional chest pressure and dyspnoea. Echocardiogram demonstrated extensive regional dysfunction with left ventricular ejection fraction (LVEF) 38%. Cardiac catheterization revealed no obstructive coronary artery disease and cardiac index 1.5 L/min/m². Cardiac magnetic resonance imaging (MRI) demonstrated diffuse late gadolinium enhancement. Positron emission tomography with fluorodeoxyglucose (FDG) (FDG-PET) computed tomography showed FDG uptake in the anteroseptal and anterior wall and no extracardiac activity. Endomyocardial biopsy (EMB) demonstrated fragments of endocardial fibrosis with mixed inflammatory infiltrate including histiocytic giant cells, which could be due to CS or GCM. She was initially treated for GCM with high dose steroids, tacrolimus, and mycophenolate mofetil. Repeat EMB was pursued and demonstrated multiple granulomas with sharp demarcation from adjacent uninvolved myocardium consistent with CS. A dual-chamber implantable cardioverter-defibrillator was placed, and immunosuppression was changed to prednisone alone with plan for infliximab.

Discussion
This case illustrates a rare presentation of fulminant isolated CS. Endomyocardial biopsy with sufficient tissue was critical to establish a diagnosis and initiate appropriate immunosuppression.

Keywords
Cardiac sarcoidosis • Giant cell myocarditis • Heart failure • Case report

Introduction
Sarcoidosis is a granulomatous disease of unknown aetiology which can affect multiple organ systems. The initial clinical manifestations of cardiac sarcoidosis (CS) are variable and can include conduction abnormalities, ventricular arrhythmias, and heart failure.1 Initial presentation with heart failure is infrequent and typically subacute; presentation with cardiogenic shock is rare. In contrast, giant cell myocarditis (GCM) is a rapidly progressive myocarditis which classically presents with acute left ventricular systolic dysfunction and ventricular arrhythmias, mimicking giant cell myocarditis.

In some cases, endomyocardial biopsy with sufficient tissue to evaluate for myocardial necrosis may be critical to differentiating between cardiac sarcoidosis and giant cell myocarditis.
systolic dysfunction, frequent ventricular arrhythmias, heart block, and cardiogenic shock often requiring mechanical circulatory support or urgent heart transplant evaluation.\textsuperscript{2} Severe CS can share clinical and histopathologic features with GCM, making diagnosis challenging. Correct diagnosis is critical to appropriate clinical management as GCM portends a poor prognosis relative to CS and necessitates a different treatment approach. This case illustrates a rare presentation of fulminant isolated CS resembling GCM.

**Timeline**

| Day 0 | Patient presents to a local hospital with 1 week of exertional chest pressure and dyspnoea. |
| Day 1 | Surface echo demonstrates extensive regional dysfunction with left ventricular ejection fraction (LVEF) of 38%. Coronary angiography reveals absence of obstructive coronary artery disease. |
| Day 2 | Patient is transferred to our institution and is initially treated with IV diuresis and guideline-directed medical therapy. |
| Day 7 | Patient develops worsening dyspnoea. Right heart catheterization demonstrates normal biventricular filling pressures and reduced cardiac index. Endomyocardial biopsy is performed. Cardiac magnetic resonance demonstrates diffuse subepicardial and mid-wall late gadolinium enhancement. Patient is started on methylprednisolone. |
| Day 8 | Pathology demonstrates fragments of endocardial fibrous tissue with associated lymphohistiocytic inflammatory infiltrate including histiocytic giant cells. Patient is started on MMF. |
| Day 9 | Patient develops runs of sustained ventricular tachycardia prompting transfer to the cardiac intensive care unit. She is started on amiodarone and tacrolimus is added to the immunosuppressive regimen. She undergoes repeat endomyocardial biopsy. |
| Day 11 | Pathology from repeat biopsy demonstrates non-necrotizing granulomas with adjacent uninvolved myocardium, consistent with cardiac sarcoidosis. MMF and tacrolimus are discontinued. |
| Day 14 | Patient undergoes dual-chamber implantable cardioverter-defibrillator placement prior to hospital discharge. |
| Two Months Post Discharge | Repeat surface echo demonstrates recovery of LVEF to 48%. Patient is initiated on infliximab and low dose methotrexate. |

**Case presentation**

A 56-year-old woman with past medical history of hypertension and dyslipidaemia on no home medications presented to the emergency department with 1 week of exertional chest pressure and dyspnoea. Initial physical examination was notable for an elevated JVP of 10 mmHg and was otherwise unremarkable. Electrocardiogram revealed prolonged PR interval, bifascicular block, and frequent pre-ventricular contractions without ischaemic ST changes. Troponin I was elevated to 8.97 (normal range 0.00–0.029 ng/mL). Initial laboratory evaluation including white blood cell count and creatinine was otherwise unremarkable; brain natriuretic peptide was not obtained on admission. She was started on a heparin drip and admitted to the cardiac intensive care unit (ICU). She underwent coronary angiography which revealed absence of obstructive coronary artery disease. Echocardiogram demonstrated moderate left ventricular hypertrophy (LVH), depressed global contractile function with near akinésis of basal wall segments, and left ventricular ejection fraction (LVEF) of 38%. She was transferred to our institution on aspirin 81 mg, losartan 25 mg, metoprolol 50 mg, and atorvastatin 20 mg for further evaluation.

Initial RHC was notable for normal biventricular filling pressures and cardiac index of 1.48 L/min/m\(^2\). Laboratory evaluation including serum protein electrophoresis (SPEP), thyroid-stimulating hormone (TSH), human immunodeficiency virus (HIV), and iron panel was unrevealing. Due to LVH noted on echocardiogram, technetium pyrophosphate scan was obtained and was equivocal for transthyretin-related amyloidosis. Endomyocardial biopsy was performed with initial right heart catheterization in accordance with AHA/ESC 2007 guidelines and demonstrated fragments of predominantly endocardial fibrous tissue with an associated lymphohistiocytic inflammatory infiltrate including histiocytic giant cells, which was felt to be suggestive of CS, though GCM could not be ruled out given paucity of myocardial involvement in the biopsy specimen (Figure 1B). Cardiac magnetic resonance imaging (MRI) demonstrated diffuse subepicardial and mid-wall late gadolinium enhancement (LGE) throughout the septal, anterior, inferior segments as well as the right ventricular free wall overall suggestive of severe biventricular myocarditis (Figure 1A).

Given the acute presentation with low cardiac index, diffuse inflammation on CMR, and equivocal EMB findings, the patient was initially treated for GCM with methylprednisolone 1 g daily and mycophenolate mofetil (MMF) 1 g twice a day. She was managed with a nitroprusside drip which was then transitioned to valsartan 40 mg twice a day. On hospital Day 9, she experienced runs of sustained ventricular tachycardia lasting several minutes which prompted a transfer to the cardiac ICU. She was started on an amiodarone drip, and tacrolimus 2 mg twice a day was added to her immunosuppressive regimen for presumed GCM. Due to uncertainty between GCM and CS and the absence of extracardiac disease, repeat right ventricular EMB with MRI guidance was pursued which demonstrated multiple well-formed non-necrotizing granulomas with sharp demarcation from adjacent uninvolved myocardium, findings consistent with CS (Figure 1C). Immunosuppression was subsequently changed to prednisone alone with plan for outpatient initiation of infliximab. A dual-chamber implantable cardioverter-defibrillator was placed for secondary prevention prior to discharge. Positron emission tomography with fluorodeoxyglucose (FDG) (FDG-PET) CT was obtained and demonstrated uptake in the anterosepal and anterior wall consistent with active sarcoidosis; there was no evidence of extracardiac activity. At discharge, her medication regimen was...
The patient was seen for follow-up in heart failure and rheumatology clinics. Five weeks following discharge, repeat echocardiogram demonstrated recovery of LVEF to 48%. Seven weeks following discharge, she was initiated on infliximab 5 mg/kg with simultaneous low dose methotrexate to prevent anti-infliximab antibody formation, and prednisone was decreased from 60 mg to 40 mg. She underwent a second loading infliximab infusion 9 weeks following discharge. Twelve weeks after discharge, her prednisone was decreased from 40 mg to 30 mg with plan for a 10 mg reduction every 4 weeks. She will continue infliximab infusions at 6-week intervals with close monitoring of cardiac function and inflammation at 6-month intervals.

Discussion

Diagnosis of CS is challenging. Evidence of non-caseating granulomas on EMB remains the established gold standard. However, EMB is limited by the invasiveness of the procedure, as well as low sensitivity due to patchy distribution of granulomas and tendency of granulomas to form in the mid-myocardium or epicardium. Furthermore, the finding of non-caseating granulomas on biopsy is not specific to CS and may be seen in several other conditions including fungal or tuberculous myocarditis and lymphomas. As demonstrated by this case, advanced CS may additionally share histopathologic features with GCM. The sarcoid granuloma is characterized by focal accumulation of inflammatory cells including lymphocytes, histiocytes, and multinucleated histiocyte giant cells. Associated myocyte necrosis is largely absent. In comparison, typical histological findings of GCM include a dense mixed inflammatory infiltrate with lymphocytes, eosinophils, histiocytes, and multinucleated histiocyte giant cells with associated myocyte necrosis. In this case, the first biopsy was a section of inflammatory cells within a granuloma, which can resemble GCM if there are no areas of surrounding intact myocytes. The two most recent guidelines on diagnosis of CS include the 2017 Guidelines for Diagnosis and Treatment of CS by the Japanese Circulation Society (JCS) and the 2014 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated with CS. Of these, the JCS guidelines allow for diagnosis of CS in the absence of histopathological confirmation. Differentiating CS from GCM is critical to appropriate clinical management as a diagnosis of GCM portends a poor prognosis relative to CS and necessitates a different treatment approach. This patient was initially treated with tacrolimus, MMF, and methylprednisolone, an immunosuppressive regimen utilized in GCM based on data extrapolated from solid organ transplant populations.

There are no clear consensus guidelines on management of CS, and overall there is limited data on efficacy of immunosuppressive regimens. In a Delphi expert study on CS, there was consensus on use of glucocorticoids as a first line immunosuppressive treatment but no agreement on second or third line therapies or use of glucocorticoid-sparing agents. Prior studies have suggested that management of CS with glucocorticoids alone is suboptimal in terms of AV nodal recovery, EF recovery, and relapse prevention.

Moderate outcomes and known risks of long-term steroid use have driven forward the consideration of glucocorticoid-sparing agents such as tumour necrosis factor (TNF) alpha inhibitors for the management of CS. Tumour necrosis factor antagonists represent a promising class of therapy given the mechanistic role of TNF in granuloma formation. In the past, use of TNF antagonists in CS has been limited to refractory cases due to concerns around potential...
treatment with infliximab. Tumour necrosis factor antagonists may partially had LVEF <45% and had >10% subsequent increase in EF after treated with infliximab included three patients with CS; all three invitational study of patients with CD4 and guideline-directed medical therapy for heart failure.

Summary of key clinical findings

| Diagnostic testing          | Notable findings                                                                 |
|----------------------------|---------------------------------------------------------------------------------|
| Laboratory evaluation      | Troponin I was elevated to 8.97 ng/mL.                                           |
|                            | SPEP, TSH, HIV, and iron panel were normal. Angiotensin-converting enzyme level was normal. |
| Electrocardiogram          | Prolonged PR interval, bifascicular block and frequent PVCs without ischaemic ST changes |
| Surface echocardiography   | Normal left ventricular size and extensive regional dysfunction with LVEF of 38% |
| Cardiac catheterization and coronary angiography | Normal biventricular filling pressures, cardiac index of 1.48 L/min/m², and absence of obstructive coronary artery disease. |
| PET-CT                     | FDG uptake in the anteroseptal and anterior wall                                    |
| Cardiac MRI                | Diffuse subepicardial and mid-wall late gadolinium enhancement throughout the septal, anterior, and inferior segments and the right ventricular free wall |
| Endomyocardial biopsy      | • First biopsy: Fragments of predominantly endocardial fibrous tissue with an associated lymphohistiocytic inflammatory infiltrate including histiocytic giant cells |
|                            | • Second biopsy: Multiple well-formed non-necrotizing granulomas with sharp demarcation from adjacent uninvoluted myocardium |

Conclusions

Severe CS can infrequently present with acute severe systolic dysfunction and ventricular arrhythmias, mimicking GCM. In this case, EMB with sufficient tissue to include adjacent myocardium was critical to establishing the diagnosis. The authors additionally report successful recovery of ejection fraction following treatment with steroids and guideline-directed medical therapy for heart failure.

Table 1 Summary of key clinical findings

Supplementary material

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

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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 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.

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Lead author biography

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Supplementary material

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