A case report of giant cell myocarditis after a syncope-related motor vehicle accident: An atypical presentation for a life-threatening condition.

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Abstract

Background
Giant cell myocarditis (GCM) is a rare and rapidly progressive disease associated with significant morbidity and mortality. Whilst patients more frequently present with acute heart failure, diagnosis is difficult due to heterogeneity in clinical presentations.

Case Summary
This case report presents a previously healthy 59-year-old Vietnamese woman who initially presented with syncope and a motor vehicle accident who developed rapid decline in left ventricular function. Her initial echocardiogram was suggestive of an infiltrative cardiomyopathy. GCM was confirmed on biopsy, and she received combined immunosuppression. Twenty-seven days following her initial presentation to hospital, she was unable to recover from severe multi-organ dysfunction and the patient was palliated and passed away.

Discussion
This case highlights the varied manner in which giant cell myocarditis may present. Even in the absence of cardiogenic shock at presentation, giant cell myocarditis should be considered in the evaluation of new cardiomyopathy of uncertainty aetiology. Diagnosis of this condition has distinct clinical implications on management and prognosis.
Learning Objectives

Case: A patient who presented with syncope and related motor vehicle accident, who subsequently died from giant cell myocarditis.

1. To recognise the heterogeneity of presentations of GCM and include GCM in the differential diagnoses of new heart failure, new cardiomyopathies, raised cardiac biomarkers, arrhythmias and LV dysfunction.
2. To understand that initial presentation of GCM may be non-specific on early ECG and TTE which may delay diagnosis.

3. To understand the role of early endomyocardial biopsy in the diagnosis of GCM in order to facilitate early treatment.

4. To understand the role of immediate initiation of immunosuppression in the management of GCM.

### Timeline of case

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Syncopal episode and motor vehicle accident. ECG normal sinus rhythm, fixed ST-elevation. TTE revealed LVEF 30%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Transferred to coronary care unit due to symptomatic hypotension and bradycardia and new bundle branch blocks.</td>
</tr>
<tr>
<td>Day 2</td>
<td>Transferred to intensive care unit for management of persistent hypotensive shock.</td>
</tr>
<tr>
<td>Day 3</td>
<td>Repeat TTE LVEF 10%.</td>
</tr>
<tr>
<td>Day 4</td>
<td>Endomyocardial biopsy performed; results consistent with giant cell myocarditis and commenced on immunosuppression.</td>
</tr>
<tr>
<td>Day 5</td>
<td>Transferred to cardiac transplant centre given potential need for ECMO or VAD. BIVAD inserted.</td>
</tr>
<tr>
<td>Day 6-20</td>
<td>Multiorgan failure ensued. Hepatic</td>
</tr>
<tr>
<td>Day</td>
<td>Event</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>18</td>
<td>LV device explanted</td>
</tr>
<tr>
<td>25</td>
<td>RV assist device explanted. Unresponsive off sedation. CT revealing large cerebral infarction.</td>
</tr>
<tr>
<td>27</td>
<td>Ongoing family discussions. Palliated and the patient passed away.</td>
</tr>
</tbody>
</table>
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Abbreviations

GCM Giant cell myocarditis
ED Emergency department
MVA Motor vehicle accident
COVID Coronavirus disease
ECG Electrocardiogram
TTE Transthoracic echocardiogram
LV Left ventricle
RV Right ventricle
EF Ejection fraction
CT Computed tomography
EMB Endomyocardial biopsy
CMR Cardiac magnetic resonance
Introduction

Giant cell myocarditis is a rare, and often rapidly progressive disease that can be fatal. The disease is characterised by myocardial necrosis, although exact pathophysiological mechanisms are unclear. The most common presentation is acute heart failure with rapid haemodynamic compromise leading to cardiogenic shock and need for mechanical circulatory support or heart transplant. Endomyocardial biopsy is the gold standard for diagnosis.

We report the case of a previously well patient who died of fulminant giant cell myocarditis who initially presented without any overt manifestations of heart failure, highlighting the heterogeneity in clinical presentations of GCM and potential for missed diagnoses that could be detrimental to treatment and prognosis.

Presentation

A 59-year-old Vietnamese woman presented to the ED following a MVA post syncopal episode in the setting of recent gastrointestinal illness. She had no preceding pre-syncope, palpitations, chest pain or dyspnoea. No urinary incontinence or tongue biting was evident. There was vomiting and abdominal pain for two days prior, without fevers or diarrhoea. She received her first COVID-19 (Pfizer) vaccine two weeks prior to the MVA. At ED triage, her heart rate was 114 beats per minute, oxygen saturation was 98% on room air, her respiratory rate was 16, her blood pressure was 120/77 and she was afebrile. She was alert, oriented, euvolaemic and had no murmurs on examination.
Past Medical History

Her medical history was significant for thalassaemia. Otherwise, she had no known cardiovascular risk factors, no prior history of seizures or significant family history.

Investigations

Initial ECG (as seen in Figure 1) in ED showed Q waves, fixed ST elevation anteriorly and low QRS voltages. Cardiac troponin I was 24 000 (normal range <12). Inflammatory markers were mildly elevated – CRP 10 and ESR 12. Her chest x-ray was unremarkable, apart from a calcified granuloma in the right apex.

Her first TTE at 20 hours (seen in Figure 2) demonstrated normal LV size; moderate-severe global systolic dysfunction; EF ~30% by visual estimation. There was mild concentric increase in wall thickness and severely reduced tissue doppler velocities. There was normal RV size and function. Mild-mod aortic regurgitation and a moderate pericardial effusion was observed. The patient deteriorated overnight with symptomatic hypotension and bradycardia to 30 beats per minute. The ECG as seen in Figure 3 revealed high grade atrioventricular block and a left bundle branch block. The initial TTE findings, in addition to worsening AV block, led to the patient being commenced on an isoprenaline infusion and transfer to the Coronary Care Unit. The patient had an expedited Cardiologist review the next morning (initial TTE performed at midnight) which resulted in expedited permanent pacemaker insertion.

The next day, the patient was persistently hypotensive to a systolic blood pressure of 60mmHg, became oliguric, and was commenced on a dopamine infusion. She had conscious, symptomatic episodes of brief accelerated idioventricular rhythm noted on telemetry. She was transferred to the Intensive Care Unit for management of persistent hypotensive shock.
TTE on day four revealed severe LV dysfunction, an EF of 10% with global hypokinesis, severely impaired RV systolic function, and a dilated inferior vena cava. Right heart function was limited to visual assessment only on subsequent TTEs due to limited imaging windows available and significant difficulties in obtaining on axis imaging. Based on the clinical course and TTE findings, a decision was made to proceed to EMB.

On day four, an EMB revealed florid infiltrate of lymphocytes, histiocytes, fewer plasma cells and scattered eosinophils, which was associated with marked oedema and cardiomyocyte necrosis. There were occasional poorly formed granulomas consisting of loose aggregates of epithelioid histiocytes, and a few multinucleated macrophages with foamy appearing cytoplasm. In summary, these features were consistent with giant cell myocarditis.

Notably, no coronary angiogram was performed due to the patient’s history, clinical assessment and imaging investigations being more supportive of a myocarditis or infiltrative pathology rather than an acute coronary syndrome (ACS). The patient had minimal risk factors for coronary artery disease and the presentation was atypical for ACS – no chest pain, with syncope and arrhythmia as presenting complaint. The global hypokinesis of the LV on the TTE could not be accounted for by a single coronary artery occlusion. The TTE also demonstrated increased LV wall thickness and markedly reduced tissue doppler velocities - which again were more consistent with infiltration. The patient’s clinical instability also dictated that the treating team perform only those procedures that will give the most benefit to the patient for the highest diagnostic yield. A coronary angiogram was not felt to be likely to give any benefit at the time for the reasons outlined above.
Management

The patient’s case was reviewed by the Immunology, Intensive Care and Cardiology team
subsequently commenced on intravenous 1g methylprednisone daily and 100mg cyclosporin
twice daily. Despite these measures, the patient developed progressively worsening lactic
acidosis and was intubated. The patient was transferred to a cardiac transplant centre.

A biventricular assist device was inserted, complicated by haemorrhage and coagulopathy
requiring massive transfusion and a thoracic washout. Whilst there was some recovery of
biventricular function with immunosuppression, the patient’s overall progress was complicated
by progressive multiorgan failure with hepatic encephalopathy, anuric renal failure requiring
dialysis, distal ischaemia of all limbs with digital gangrene, and presumed bowel ischaemia.
Immune thrombocytopenia developed which was treated with intravenous immunoglobulin and
plasma exchange. Polymicrobial sepsis with Pseudomonas bacteraemia and Candidaemia was
treated with meropenem, vancomycin and caspofungin.

On day 18, the LV assist device was explanted during a redo-sternotomy and a tissue aortic valve
replacement was performed due to severe aortic valve insufficiency. The RV assist device was
explanted percutaneously on day 25. A cerebral infarction in the anterior and right middle
cerebral artery territory was seen on a CT scan on day 25, and the patient was unresponsive off
sedation. The prognosis of functional recovery in the setting of severe multi-organ dysfunction
was poor. After a family meeting on day 27, the decision was made to palliate, and the patient
passed away on the same day.
Discussion

GCM is a rare and often fatal type of myocarditis\textsuperscript{1,3}. The exact underlying pathophysiological mechanisms remain unclear. The clinical course of GCM is usually characterized by acute or fulminant deterioration in LV systolic function despite standard HF treatment, frequent ventricular arrhythmias, and heart block\textsuperscript{3}. A multicenter international registry of 63 patients with GCM revealed that 75\% presented with HF, 14\% with ventricular tachycardia, 6\% mimicked acute myocardial infarction, and 5\% had complete heart block \textsuperscript{1}. Our case reports a previously well patient who died of fulminant GCM initially presenting without overt manifestations of heart failure, highlighting the heterogeneity in clinical presentations of GCM and the potential for missed, or delayed diagnosis, which is detrimental to treatment and prognosis. While the patient was in sinus rhythm on ED presentation, it is possible that intermittent complete heart block may have caused the initial presentation of syncope.

EMB is the gold standard for diagnosis \textsuperscript{2}. Alternatively, CMR imaging provides supportive evidence of myocarditis when EMB is not available. CMR imaging is indicated in patients with suspected myocarditis with elevated troponin level and/or ventricular dysfunction without a clear cause.

Combination immunosuppressive therapy has led to a paradigm shift in the management of GCM resulting in an improvement in overall and transplant-free survival \textsuperscript{4}. Among 22 patients treated with immunosuppressive medications that included cyclosporine, the average transplant-free survival was 13 months compared with only three months among 30 patients who did not receive therapy. A benefit from immunosuppressive therapy was also suggested by a study of 32 patients with GCM, including 26 patients treated with combined immunosuppression (two to
four drugs; including cyclosporine in 20 patients). Among the 26 patients treated with 
immunosuppression, the Kaplan-Meier estimate of transplant-free survival from diagnosis was 
77 percent at one year, 63 percent at two years, and 63 percent at five years. This case of GCM 
was reviewed by multiple specialty teams, who unanimously felt that the corticosteroid and 
cyclosporin combination was adequate for initial treatment. The patient deteriorated and was 
transferred to allow initiation of mechanical circulatory support and transplant before further 
immunosuppressive agents could be added.

A recent review of both human and animal models of GCM suggests myocardial inflammation is 
mediated by T-lymphocytes and giant cells. T-cell targeted therapy is now included as an 
adjunct to traditional immunosuppressive therapy (steroids/cyclosporine), including treatment 
with muromonab-CD3, antithymocyte globulin (ATG) or alemtuzumab. The first eleven patients 
in a prospective GCM registry were treated with cyclosporine and corticosteroids, with or 
without muromonab-CD3, had an overall survival of 91% at one year, with one death and two 
patients requiring transplantation within the first month. Alemtuzumab has also been 
successfully used in a case report of post-cardiac transplant GCM refractory to methylprednisone 
and ATG, resulting in symptomatic and histological resolution.

Conclusions

In conclusion, GCM should be suspected in patients with or without cardiac signs and symptoms, 
who have a rise in cardiac biomarkers, ECG changes suggestive of acute myocardial injury, 
arrhythmias, or abnormalities of LV systolic function, particularly if the clinical findings are new 
and unexplained. Establishing the diagnosis early in the disease course is critical for management
as early intensive immunosuppression may improve prognosis and lead to longer term transplant-
free survival.

4 Patient Consent

The deceased patient's family have read the article contents and have consented to the material
about the patient appearing in an EHJ publication and give permission to proceed in accordance
with COPE guidelines.
Reference List


Figure 1. Initial ECG. Normal sinus rhythm with poor R wave progression in praecordial leads, Q waves, fixed ST elevation anteriorly and low QRS voltages.

Figure 2. Initial TTE at 20 hours. Normal LV size; moderate-severe global systolic dysfunction; EF ~30% by visual estimation. Mild concentric increase in wall thickness and severely reduced tissue doppler velocities. Normal RV size and function. Mild-mod aortic regurgitation and a moderate pericardial effusion was observed.

Figure 3. Repeat ECG. High grade atrioventricular block and left bundle branch block.

Figure 4. Repeat TTE at day four. Severe LV dysfunction, EF 10% with global hypokinesis, severely impaired RV systolic function, and a dilated inferior vena cava.