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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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 GCM 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.

Keywords
Heart failure • Giant cell myocarditis • Complete heart block • Case report

ESC Curriculum
6.1 Symptoms and signs of heart failure • 6.2 Heart failure with reduced ejection fraction • 6.4 Acute heart failure • 6.5 Cardiomyopathy • 7.3 Critically ill cardiac patient

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

• To recognize the heterogeneity of presentations of giant cell myocarditis (GCM) and include GCM in the differential diagnoses of new heart failure, new cardiomyopathies, raised cardiac biomarkers, arrhythmias, and left ventricular dysfunction.
• To understand that initial presentation of GCM may be non-specific on early electrocardiogram (ECG) and transthoracic echocardiogram, which may delay diagnosis.
• To understand the role of early endomyocardial biopsy in the diagnosis of GCM in order to facilitate early treatment.
• To understand the role of immediate initiation of immunosuppression in the management of GCM.

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Introduction

Giant cell myocarditis is a rare and often rapidly progressive disease that can be fatal. The disease is characterized 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 giant cell myocarditis (GCM) and potential for missed diagnoses that could be detrimental to treatment and prognosis.

Timeline

| Timeline of case          | Day 0 | Syncopal episode and motor vehicle accident. Electrocardiogram normal sinus rhythm, fixed ST elevation. Transthoracic echocardiogram (TTE) revealed left ventricular ejection fraction (LVEF) 30%. |
|--------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          | Day 1 | Transferred to coronary care unit due to symptomatic hypotension and bradycardia and new bundle branch blocks.                                                                                                                                                    |
|                          | Day 2 | Transferred to intensive care unit for management of persistent hypotensive shock.                                                                                                                                                                                  |
|                          | Day 3 | Repeat TTE LVEF 10%.                                                                                                                                                                                                                                                |
|                          | Day 4 | Endomyocardial biopsy performed; results consistent with giant cell myocarditis and commenced on immunosuppression.                                                                                                                                                 |
|                          | Day 5 | Transferred to cardiac transplant centre given potential need for extracorporeal membrane oxygenation or ventricular assist device. Biventricular assist device inserted.                                                                                   |
|                          | Days 6–20 | Multigener failure ensued. Hepatic encephalopathy, anuric renal failure requiring dialysis, distal ischaemia of limbs, bowel ischaemia, immune thrombocytopenia, polymicrobial sepsis.                                                                 |
|                          | Day 18 | LV device explanted.                                                                                                                                                                                                                                               |
|                          | Day 25 | Right ventricular assist device explanted. Unresponsive off sedation. Computed tomography imaging revealing large cerebral infarction.                                                                                                                                |
|                          | Day 27 | Ongoing family discussions. Palliated and the patient passed away.                                                                                                                                                                                                   |

Case presentation

A 59-year-old Vietnamese woman presented to the emergency department (ED) following a motor vehicle accident (MVA) post-syncopal episode in the setting of recent gastrointestinal illness. She had no preceding pre-syncpe, palpitations, chest pain, or dyspnoea. No urinary incontinence or tongue biting was evident. There was vomiting and abdominal pain for 2 days prior, without fever or diarrhoea. She received her first COVID-19 (Pfizer) vaccine 2 weeks prior to the MVA. At ED triage, her heart rate was 114 beats per min, 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, euvalaemic, and had no murmurs on examination.

Past medical history

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

Investigations

Initial electrocardiogram (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—creactive protein 10 and erythrocyte sedimentation rate 12. Her chest x-ray was unremarkable, apart from a calcified granuloma in the right apex.

Her first TTE at 20 h (seen in Supplementary material online, Figure S2) demonstrated normal left ventricle (LV) size; moderate-severe global systolic dysfunction; and ejection fraction (EF) ~30% by visual estimation. There was mild concentric increase in wall thickness and severely reduced tissue Doppler velocities. There was normal right ventricle (RV) size and function. Mild-mod aortic regurgitation and a moderate pericardial effusion were observed. The patient deteriorated overnight with symptomatic hypotension and bradycardia to 30 beats per minute. The ECG as seen in Figure 2 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 60 mmHg, 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 4 (as seen in Supplementary material online, Figure S4) 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 endomyocardial biopsy (EMB).

On day 4, 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 the 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 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 and was subsequently commenced on intravenous 1 g methylprednisone daily and 100 mg 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 aeruginosa* 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 computed tomography 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. 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. 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. 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 and should be considered early in infiltrative cardiomyopathies. Alternatively, cardiac magnetic resonance (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. Among 22 patients treated with immunosuppressive medications that included cyclosporine, the average transplant-free survival was 13 months compared with only 3 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 1 year, 63 percent at 2 years, and 63 percent at 5 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 11 patients in a prospective GCM registry were treated with cyclosporine and corticosteroids, with or without muromonab-CD3, had an overall survival of 91% at 1 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 histologic 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.

**Lead author biography**

Lily Pham is an Australian Basic Physician Trainee currently completing a Masters in Public Health and Tropical Medicine (MPHTM) at James Cook University, with an interest in global health equity and diversity in medical leadership. She currently sits on the Royal Australasian College of Physicians Queensland Trainees’ Committee and is an Associate Lecturer at the University of Queensland. Lily believes that espousing diversity, equity, and inclusion in healthcare and research leads to a cultural competency that enables clinicians to offer services that recognize and address the unique social, cultural, economic, and linguistic needs of their patients.

**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 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.

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