Giant cell myocarditis: challenge of mechanical circulatory support (RCD code: III-1B.1.o)

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Abstract
We report the case of a young adult male who presented with acute fulminant myocarditis, deteriorated rapidly despite intra-aortic balloon pump and inotropic support, and received a HeartMate II continuous flow left ventricular assist device (LVAD) as a bridge to heart transplantation. The left ventricular apical core biopsy showed giant cell myocarditis. Despite treatment with steroids and immunosuppression, there was progressive left and right ventricular dysfunction, culminating in asystole and a Fontan-like circulation dependent on LVAD flow. He developed severe right heart failure with ascites and pleural effusions, refractory to pharmacological therapy, and ultimately died due to complications of renal failure. We review the diagnosis, natural history and management of giant cell myocarditis, with a focus on challenges raised by mechanical circulatory support in this patient group. JRCD 2013; 1 (3): 109–112

Key words: Giant cell myocarditis, left ventricular assist device

CASE REPORT

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Case presentation
A young adult male, previously fit and well, presented to his primary care physician with a short history of exertional breathlessness. He was found to be tachycardic and referred for an electrocardiogram (ECG). This showed non-specific ST segment and T-wave abnormalities. The cardiac physiologist performed a transthoracic echocardiogram. The left ventricle (LV) was non-dilated with severe concentric left ventricular hypertrophy and global hypokinesia of all LV segments, resulting in severe impairment of LV systolic function (Figure 1). He was admitted for further assessment. There was clinical evidence of acute cardiogenic pulmonary oedema with elevated venous pressure and bilateral crackles at the lung bases. Cardiac troponin-I was mildly elevated at 0.18 mg/L. His condition deteriorated rapidly with hypotension and biochemical evidence of renal and liver dysfunction, necessitating transfer to the regional advanced heart failure centre for ongoing management.

His condition continued to deteriorate over the following 24 hours with progressive end-organ dysfunction despite intra-aortic balloon pump support and escalating inotropic support. A multi-disciplinary team of heart failure cardiologists, cardiac surgeons and cardiac anaesthetists was convened. It was agreed that he was unlikely to survive without mechanical circulatory support. He was felt to be in class 2 of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale. His echocardiographic images were reviewed in detail and there was no evidence of right ventricular dysfunction. The working diagnosis was acute myocarditis and a decision was made to implant a long-term left ventricular assist device (LVAD, HeartMate II, Thoratec, CA, USA) as a bridge to cardiac transplantation. The total time between initial presentation and LVAD implantation was only 4 days.

The operation and early post-operative period were uneventful with the exception of an episode of atrial flutter that was successfully treated with DC cardioversion. There was excellent recovery of renal and hepatic function. Three days after initiation of LVAD support, the patient was extubated, weaned from inotropic support and left the intensive care unit. He started to mobilize and participate with physiotherapy. At this stage, the left ventricular core biopsy sent from the operating room at the time of LVAD inflow cannula placement had been analysed by the pathologists. The histological images in figure 2 show multinucleate giant cell formation and myocyte disarray that is characteristic of giant cell myocarditis (GCM).

Review of literature
GCM is rare. The first worldwide registry established in 1995 only identified 63 definite cases. The mean age at presentation was 43 years and both sexes were affected equally.[1] In the largest published case series, 32 biopsy-proven cases were identified.
between 1999 and 2011 at a national referral centre in Finland (population 5.2 million), equating to an incidence of 0.0003 cases per 1000 person-years.[2] An identical estimate was obtained in a post-mortem study of deaths due to myocarditis between 1990 and 1998 in Finland, with evidence of GCM in 5.6% of 639 cases of fatal myocarditis during 141,438,176 person-years of records.[3,4] Both estimates are vulnerable to under-reporting and likely to be biased toward the severe end of the disease spectrum.

In the majority of cases, GCM presents with aggressive fulminant myocarditis leading to acute heart failure and rapid progression to cardiogenic shock. Ventricular arrhythmias and high-grade atrioventricular block are common and may be the reason for presentation.[1] GCM is believed to be an auto-immune condition mediated by T-lymphocytes and 20% of cases are associated with other auto-immune conditions, most frequently inflammatory bowel disease.[1,5] The prognosis is very poor. In the multi-center GCM study of 63 cases, 89% of affected individuals died or underwent heart transplantation and median transplant-free survival was only 5.5 months from symptom onset.[1] In the most recent series of 32 biopsy-proven cases in Finland, 47% of affected individuals died or underwent heart transplantation a median of 11 months from symptom onset.[2]

Diagnosis is challenging, largely due to the fulminant nature of GCM and the requirement for myocardial tissue for pathological examination. GCM must be distinguished from lymphocytic myocarditis, granulomatous myocarditis, other systemic inflammatory disorders, hypersensitivity reactions and complications of infectious diseases such as measles or syphilis.[6] As indicated in epidemiological studies, the diagnosis is frequently made in retrospect, either at autopsy or during pathological examination of the recipient heart after cardiac transplantation. According to a joint United States and European scientific statement, endomyocardial biopsy should be performed in the setting of unexplained, new-onset heart failure of less than 2 weeks’ duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise (Class of Recommendation I, Level of Evidence B).[7] If undertaken, the sensitivity for endomyocardial biopsy for GCM is 80–85% in individuals who die or subsequently undergo transplantation.[8]

There are limited options for treatment and no randomized data to guide physicians. In the multi-center GCM study, median time from diagnosis to either death or transplantation was 3.0 months in patients who did not receive immunosuppression. Treatment with steroids was not associated with higher transplant-free survival (median survival 3.8 months, P = 0.68). However, addition of other immunosuppressive medications alongside steroid, either anti-thymocyte globulin, azathioprine or ciclosporin was associated with a higher median transplant-free survival (12.3 months, P = 0.001).[1,9] Combined immunosuppression has become standard practice in many countries. Three agents are typically used in combination; steroid, ciclosporin and either azathioprine or mycophenolate mofetil.[2] Using this treatment regime in 26 patients diagnosed with GCM on endomyocardial biopsy, 17 patients survived free of heart transplantation after a median follow-up of 35 months, eight patients underwent cardiac transplantation and only one patient died.[2]

Heart transplantation has traditionally been the definitive treatment option in GCM. Post-transplant mortality in GCM is similar
to alternate transplant indications, with a 30-day post-transplant mortality of 14.7% in the multi-centre GCM study.[1,10] GCM may recur in the transplanted heart. Giant cell infiltrates were seen on post-transplant endomyocardial biopsy in 26% of patients after a mean time of 3 years post-transplant, although most responded to increased immunosuppression and only one patient (3%) died of recurrent GCM in this series.[1] The era of mechanical circulatory support has provided a different perspective on the natural history of GCM. There are multiple case reports of patients that have been bridged to either recovery or transplantation using a variety of mechanical circulatory support techniques in the presence or absence of immunosuppression.[11,12] Other groups have described successful bridging to transplantation with mechanical circulatory support involving up to three different types of ventricular assist device.[13,14]

### Patient Management and Follow-up

Despite concerns about the possibility of increased susceptibility to infection with a recently implanted LVAD, a decision was made to institute immunosuppression with a combination of oral prednisolone and mycophenolate mofetil. Sadly, there was progression of the underlying disease process despite immunosuppression. This was initially manifest as episodes of ventricular tachycardia, episodes of third degree atrioventricular block and broadening of the intrinsic QRS complex. Despite these arrhythmias, there was good LVAD flow and adequate LV filling. After several days, the rhythm deteriorated to agonal complexes and ultimately asystole. Echocardiography revealed a static heart. A decision was made to stop immunosuppressive therapy and taper the steroid dose as the prospect of myocardial recovery was felt to be negligible. From this time onwards, the patient was entirely dependent on LVAD flow with a passive pulmonary circulation, a situation akin to Fontan physiology.

The patient started to develop features of right heart failure. This was initially manifest as abdominal swelling and the development of a large right pleural effusion (figure 3) associated with abnormal liver function tests and a rising INR. This right heart failure was refractory to conventional therapies including continuous infusion of intravenous Furosemide, intravenous Dopamine and intermit-
tention to fluid balance must therefore be meticulous and may require haemofiltration in addition to fluid restriction and aggressive diuretic therapy. Importantly, maintaining a low PVR will minimize the requisite CVP. Once right heart failure become established, a vicious circle of renal venous congestion, reduced glomerular filtration and salt/water retention may develop and become almost impossible to break.

Finally, our case raised important issues in relation to communication and end-of-life care. Providing clear, consistent and accurate information to the patient and family about treatment options and prognosis was difficult because of the complexity of the case, the large number of healthcare professionals involved in management and uncertainty amongst the clinical team as to the optimal treatment strategy. It is important to be honest and direct with patients and their families throughout the illness, including areas of uncertainty. During any given day or week, it may be helpful for a single individual to assume responsibility for communication to ensure message continuity. Sadly, a proportion of patients will die despite mechanical circulatory support. End-of-life care for these patients will be unfamiliar to most healthcare professionals and survival for long periods of time in either asystole or persistent ventricular fibrillation is not unusual. In addition, it may be difficult to recognise the point at which the focus of treatment should become palliative and clinicians should be cognisant of the strong bond that is likely to develop with their patient and the potential impact of this bond on decision-making.

Conclusions

GCM is a rare cause of fulminant myocarditis and will frequently progress to severe biventricular failure. Physicians and surgeons should be aware of this diagnostic possibility when considering mechanical circulatory support. If GCM is confirmed, they should consider immunosuppression and early transplantation in the event of continued deterioration. If mechanical support is utilized, they must be alert to the development of right heart failure. Clear communication and effective palliation of symptoms is essential for patients who exhibit progressive and irreversible deterioration.

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