Images in cardiovascular medicine

Giant cell myocarditis successfully treated with antithymocyte globuline and extracorporeal membrane oxygenation for 21 days
Enrico Ammirati, Fabrizio Oliva, Oriana Belli, Edgardo Bonacina, Patrizia Pedrotti, Fabio Maria Turazza, Alberto Roghi, Roberto Paino, Luigi Martinelli and Maria Frigerio

A 31-year-old man presenting with cardiogenic shock and left ventricular ejection fraction of 10% received the diagnosis of giant cell myocarditis by endomyocardial biopsy. The patient was successfully treated with high-dose inotropes, intra-aortic balloon pump and venaoteral extracorporeal membrane oxygenation for 21 days associated with combined immunosuppression (thymoglobulin, steroids, cyclosporine).

Immunosuppression including thymoglobulin is the regimen associated with the highest probability of recovery in case of giant cell myocarditis. Immunosuppression needs time to be effective; thus, hemodynamic support must be guaranteed. In the present case, we observed that full recovery can be obtained up to 21 days of support with extracorporeal membrane oxygenation and adequate immunosuppression.

Summary
A 31-year-old man presenting with cardiogenic shock due to giant cell myocarditis (GCM) was successfully treated with high-dose inotropes, intra-aortic balloon pump (IABP) and venaoteral extracorporeal membrane oxygenation (ECMO) for 21 days and combined immunosuppression (thymoglobulin, steroids, cyclosporine). Immunosuppression needs time to be effective. In the present case, we observed that full recovery can be obtained up to 21 days of support with ECMO and adequate immunosuppression.

Case report
In November 2012, a 31-year-old man with multiple autoimmune disorders (thyroiditis, ulcerative colitis, hepatitis) was hospitalized because of progressive dyspnoea. ECG showed sinus tachycardia and ST-elevation in D1–aVL. Echocardiography showed left ventricular (LV) dysfunction [LV ejection fraction (LVEF) 30%]. Coronary angiography was normal. Because of impending cardiogenic shock, on day 2 the patient was transferred to our hospital. High-dose inotropes (epinephrine and dopamine) and IABP obtained temporary stabilization. On day 3, myocardial injury (N-terminal of the prohormone brain natriuretic peptide 32 126 ng/l, high-sensitivity troponin T 2065 ng/l), systemic inflammatory response (C-reactive protein 24.6 mg/dl) and initial multisystem organ failure were observed. According to the European Society of Cardiology position statement on myocarditis, right ventricular endomyocardial biopsy was performed, providing the diagnosis of GCM, on the basis of myocyte damage and inflammation with multinucleated giant cells and eosinophils (Fig. 1a).

Because of further deterioration of cardiac function (LVEF 10%) and recurrent sustained ventricular tachycardias (SVT), mechanically assisted ventilation and venaoteral ECMO were promptly instituted. Immunosuppression with thymoglobulin, intravenous steroids and oral taper, and cyclosporine microemulsion were started. On day 4, the patient was weaned off the ventilator, but IABP and ECMO had to be maintained because of persistent severe biventricular dysfunction and hypotension. Meanwhile, on day 17, the patient was enrolled in the high-urgency national heart transplantation (HTx) waiting list. In the next few days, myocardial function began to improve, with LVEF increasing up to 50%. IABP and ECMO were removed on day 21, inotropes were stopped, and standard heart failure therapy with enalapril and bisoprolol was started, while maintaining immunosuppression (cyclosporine 3.5 mg/kg/day, prednisone 0.5 mg/kg/day). The patient was removed from the HTx list and discharged on day 34. One week later, cardiac magnetic resonance showed normal systolic function (LVEF 60%) with areas of late gadolinium enhancement and myocardial oedema in the subepicardium (Fig. 1b; supplemental video 1). Positive Antinuclear
Fig. 1

(a) Endomyocardial biopsy sample highlighting the diagnostic hallmarks of giant cell myocarditis: myocyte damage, widespread inflammatory infiltrates, presence of multinucleated giant cells (green arrows) and eosinophils (white arrow). (b) At discharge, cardiac magnetic resonance showed diffuse areas of myocardial oedema (green arrows) in the subepicardium on the basis of T2-weighted oedema images (on the left). Signs of myocardial inflammation remained despite the recovery of the systolic function. Diffuse areas of late gadolinium enhancement (red arrows) were evident in epicardial regions coupled with areas of inflammation. (c) Three months after discharge, cardiac magnetic resonance showed persistence of more localized areas of myocardial oedema (green arrows on the left) in the subepicardium on the basis of T2-weighted oedema images in two-chamber view (on the left). A new small aneurismatic area appeared on the short-axis view, potentially justifying the propensity for arrhythmias (green arrow on the right).
Nevertheless, Venoarterial extracorporeal membrane oxygenation (ECMO) duration and immunosuppressive regimen in previous cases of giant cell myocarditis reported in the literature

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>ECMO duration</th>
<th>Final outcome</th>
<th>Immunosuppressive treatment regimen</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazebroek MR (2013)</td>
<td>11 days</td>
<td>Biventricular assist device and subsequent heart transplantation (HTx)</td>
<td>Methylprednisolone + cyclophosphamide</td>
<td>International Journal of Cardiology</td>
</tr>
<tr>
<td>Yeen WC (2011)</td>
<td>8 days</td>
<td>Recovery</td>
<td>Antithymocyte globuline + cyclosporin + methylprednisolone</td>
<td>Interactive Cardiovascular and Thoracic Surgery</td>
</tr>
<tr>
<td>Seeburger J (2010)</td>
<td>26 h</td>
<td>HTx</td>
<td>Intravenous immunoglobulin</td>
<td>The Canadian Journal of Cardiology</td>
</tr>
<tr>
<td>Weidenbach M (2008)</td>
<td>5 days</td>
<td>HTx</td>
<td>No immunosuppressive treatment</td>
<td>Journal of Heart and Lung Transplantation</td>
</tr>
<tr>
<td>Le Guyader A (2008)</td>
<td>4 days</td>
<td>HTx</td>
<td>No immunosuppressive treatment</td>
<td>Interactive Cardiovascular and Thoracic Surgery</td>
</tr>
<tr>
<td>Ankersmit HJ (2006)</td>
<td>7 days</td>
<td>Recovery</td>
<td>Antithymocyte globuline + cyclosporin + prednisolone</td>
<td>The Thoracic and Cardiovascular Surgeon Transplant International</td>
</tr>
<tr>
<td>Toscano G (2014)</td>
<td>15 days</td>
<td>HTx</td>
<td>Cyclosporin + methylprednisolone + azathioprine</td>
<td>Current case</td>
</tr>
<tr>
<td>Ammirati E (2014)</td>
<td>21 days</td>
<td>Recovery</td>
<td>Antithymocyte globuline + cyclosporine + methylprednisolone</td>
<td></td>
</tr>
</tbody>
</table>

Table 1

antibodies, anti-native DNA and anti-double stranded DNA were found (immunologic criteria), which, together with presence of hematologic disorder and serositis, suggested the diagnosis of systemic lupus erythematosus.

GCM is a life-threatening condition attributed to a T-cell-mediated myocardial inflammation. Up to 20% of cases are associated with autoimmune disorders, with inflammatory bowel disease being the most frequent condition. It must be noted that few single case reports have suggested that viral infections can also have a role in GCM. Immunosuppression is recommended, although no standard therapy protocol has been defined. Recurrent GCM has been reported after immunosuppression withdrawal, and also in the transplanted heart. We choose aggressive induction because of severe clinical and histopathological picture, and a maintenance regimen that is generally well tolerated in the long term.

GCM is a disease of the relatively young, with acute heart failure as the most frequent clinical feature. Severe low output syndrome may require circulatory support to ensure patient survival, buying time to wait for myocardial recovery, or for a donor heart when irreversible myocardial damage has occurred. The combined immunosuppression including thymoglobulin, intravenous steroids and oral taper, and cyclosporine appears as the treatment associated with the highest probability of recovery. Nevertheless, immunosuppressive treatments need time to be effective, and in the meanwhile hemodynamic support must be guaranteed. ECMO appears a suitable support both as a bridge to HTx or to recovery. In Table 1, we summarize the recent experiences and the duration of ECMO support in patients with GCM treated with ECMO. In all cases in which a full recovery was obtained, thymoglobulin was associated with cyclosporine and steroids and ECMO was maintained for at least 1 week, similarly to our case. To the best of our knowledge, this is one of the longest ECMO supports described with full recovery in a patient with a GCM.

Arrhythmias (atrioventricular blocks, SVT) are also common signs of GCM presentation. Moreover, up to 60% of transplant-free survivors experienced SVT, suggesting considering a prophylactic implantable cardioverter-defibrillator. In fact, 3 months after discharge, our patient also experienced a SVT that was hemodynamically well tolerated and resolved with external Direct current shock. Endomyocardial biopsy was negative, no signs of recurrent cardiac dysfunction were observed, and follow-up cardiac magnetic resonance showed patchy myocardial texture, with fibrosis and a small aneurismal area within LV myocardial walls (Fig. 1c), justifying the propensity for arrhythmias even in the absence of recurrent inflammation. Thus, an implantable cardioverter-defibrillator was implanted. At 21-month follow-up, the patient is fine, New York Heart Association class 1, without relapse of GCM or episodes of arrhythmias, maintaining immunosuppression with cyclosporine (100 mg twice daily; 2.7 mg/kg/day) associated with prednisone (7.5 mg once daily).

Acknowledgements

Enrico Ammirati received financial support from the ‘Giovane Ricercatore 2009 Grant’ from Italian Health Ministry (project code GR-2009-1608780).

There are no conflicts of interest.

References