Mechanical Circulatory Support Combined With Immunosuppression for the Treatment of Giant Cell Myocarditis
— A Single-Center Experience in Japan —

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Background: The therapeutic strategy for giant cell myocarditis (GCM) remains controversial, so we reviewed the clinical status of Japanese patients with GCM.

Methods and Results: We retrospectively reviewed 6 consecutive patients with GCM requiring percutaneous mechanical circulatory support (p-MCS), with 3 further requiring ventricular assist devices. One patient died during p-MCS. Cardiac function improved in the other 5 with immunosuppressive therapy, but only 3 patients treated with dual immunosuppressants, including cyclosporine (CyA), achieved >1-year survival.

Conclusions: The prognosis of patients with fulminant GCM is poor, but a treatment that combines MCS and early administration of CyA-based immunosuppressants will be useful.

Key Words: Giant cell myocarditis; Immunosuppressants; Mechanical circulatory support

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Giant cell myocarditis (GCM) typically develops in young-to-middle-aged healthy adults and is associated with a high mortality rate. On histological examination, GCM is characterized by the presence of a large number of multinucleated giant cells in both ventricles, with the high incidence of autoimmune diseases in patients with GCM supporting the theory that GCM itself is an autoimmune disorder. GCM is usually treated with cyclosporine (CyA)-based immunosuppressive therapy. As with other types of myocarditis, in cases of fulminant GCM, temporary percutaneous mechanical circulatory support (p-MCS) and/or a paracorporeal ventricular assist device (pVAD) are necessary. In Western countries, heart transplantation (HTx) is performed if severe cardiac dysfunction persists despite conservative treatment. However, the recurrence rate of GCM is high after HTx. This is an important issue to consider because of the difficulty of establishing HTx candidacy in Japan due to a severe shortage of donor hearts. In fact, the therapeutic strategy for GCM remains controversial in Japan, where donor heart availability is very low. Our case series is important in this regard because it is the first to review the clinical and disease outcomes of patients with GCM treated using immunosuppressive therapy while on MCS in Japan.

Methods

Patient Population
We retrospectively reviewed 6 consecutive patients (3 males) who were diagnosed with GCM between April 2010 and March 2018. All patients were adults, >18 years of age, with a median age of 59.5 years. In all patients, the GCM diagnosis was confirmed by histological examination of endocardial samples of the right ventricle or left ventricular (LV) apex. Clinical parameters, including patient demographics, laboratory data, echocardiography data, treatment
course, and outcomes, were retrospectively assessed through a review of patients’ medical records.

Statement on Ethics
Our case series study was exempted from the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” established by the Japanese government. As per the institutional ethics guidelines, however, informed consent for publication was obtained from the patients or their next of kin.

MCS Strategies for Patients With GCM
All patients initially received temporary p-MCS, such as intra-aortic balloon pumping (IABP) and/or percutaneous extracorporeal membrane oxygenation (p-ECMO), as a life-saving intervention. If the systemic condition was not stabilized after short-term support, a pVAD was implanted. The Nipro-Toyobo VAD (Nipro-VAD, Nipro, Osaka, Japan) was used for LV support and ECMO followed by implantation of the Nipro-Toyobo VAD for right ventricular support.

Results
Baseline Clinical Characteristics and Presentation
Patients 2, 4, and 5 had concurrent autoimmune diseases, comprising myasthenia gravis, hyperthyroidism and polyarthritis with alopecia. All patients were screened for antinuclear antibodies, with patient 4 testing positive for anti-centromere antibody, without exhibiting any symptoms of scleroderma (Table 1).

Blood serum analyses revealed a mild chronic elevation of creatine kinase-MB isoenzyme (CK-MB) level (range, 18–1131 IU/L), with no apparent peak value detected. No case of refractory ventricular arrhythmia was identified.

However, patients 1, 2, 3, and 5 presented with impaired cardiac conduction, requiring temporary or permanent pacemaker implantation, without a defibrillator. Echocardiography was completed in all 6 patients before p-MCS. The median LV end-diastolic dimension (LVEDd) was 54.5 mm (range, 40–56 mm), with a median LV ejection fraction (LVEF) of 14% (range, 10–39%).

Treatment Course and Immunosuppression
All 6 patients experienced cardiogenic shock and received temporary p-MCS at a median of 17 days after the onset of symptoms. Patients 2, 3, and 5 ultimately required a pVAD. Of note, no patient was further treated with an implantable LV assist device (LVAD) or HTx. Patient 3 required biventricular support, with the right VAD established at the time of LVAD (Table 1).

With regard to immunosuppressive therapy, only patient 6 was treated with steroids and CyA, with a target trough level of 100–150 ng/mL, prior to MCS. However, during MCS, all patients received steroid therapy. The exception of patient 2, patients were first treated with high-dose corticosteroid pulse therapy, followed by oral steroid therapy. Patients 4, 5, and 6 were additionally started on oral CyA, with a target trough level of 100–150 ng/mL, while on MCS, with this dual immunosuppressive therapy maintained after MCS removal (Table 2).

Patients 4 and 6 continue to be managed with low-dose steroid and CyA therapy via the outpatient clinic, with a target trough level of 50 ng/mL and 100 ng/mL, respectively. Patient 4 used 5 mg of prednisolone (PSL) as a maintenance dose, discontinuing PSL at 2 years after GCM onset.

Patients 1, 2, 3, and 5 received intravenous immunoglobulin treatment; of note, none of these patients were treated using muromonab-CD3 or anti-thymocyte globulin. Patients 2, 4, 5, and 6 were treated using angiotensin-
serum levels of troponin T (Figure D), and the patients were weaned from MCS, after a median period of 22 days (range, 8–78 days). Recurrence of GCM was identified in patient 5, early after LVAD removal, but without new injury to the myocytes detected. The patient was successfully treated using high-dose corticosteroid pulse therapy. Ultimately, for all 3 patients (2, 3, and 5) treated using VAD, although hemodynamics were stable for a while, cardiac function gradually deteriorated after VAD removal and all 3 patients died of multiple organ failure due to low converting enzyme inhibitors after their systemic condition stabilized, with patients 4 and 6 further treated using β-blockers.

**Outcomes and Adverse Events**

Patient 1 did not recover cardiac function and died from multiple organ failure while on p-ECMO support, on day 18 after initiation of p-MCS treatment (Table 1). After immunosuppressive therapy, cardiac function improved in the remaining 5 patients (Figure A–C), with a decrease in serum levels of troponin T (Figure D), and the patients were weaned from MCS, after a median period of 22 days (range, 8–78 days). Recurrence of GCM was identified in patient 5, early after LVAD removal, but without new injury to the myocytes detected. The patient was successfully treated using high-dose corticosteroid pulse therapy. Ultimately, for all 3 patients (2, 3, and 5) treated using VAD, although hemodynamics were stable for a while, cardiac function gradually deteriorated after VAD removal and all 3 patients died of multiple organ failure due to low

**Table 2. Imunosuppressant Regimens**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Time from the initial symptoms to immunosuppression (days)</th>
<th>Before p-MCS</th>
<th>While on p-MCS</th>
<th>While on VAD</th>
<th>After MCS weaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>None</td>
<td>mPSL → hydrocortisone</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>None</td>
<td>mPSL</td>
<td>None</td>
<td>mPSL (secondary pulse therapy for eosinophil infiltrate)</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>None</td>
<td>None</td>
<td>mPSL → PSL</td>
<td>PSL</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>None</td>
<td>mPSL → PSL+CyA</td>
<td>–</td>
<td>PSL+CyA</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>None</td>
<td>None</td>
<td>mPSL → PSL+CyA</td>
<td>mPSL (secondary pulse therapy for GCM recurrence) → PSL+CyA</td>
</tr>
<tr>
<td>6</td>
<td>394</td>
<td>mPSL → PSL+CyA</td>
<td>mPSL → PSL+CyA</td>
<td>–</td>
<td>PSL+CyA</td>
</tr>
</tbody>
</table>

CyA, oral cyclosporine; GCM, giant cell myocarditis; p-MCS, percutaneous mechanical circulatory support; mPSL, methylprednisolone pulse treatment; PSL, oral prednisolone; VAD, ventricular assist device.

![Figure](image-url)

**Figure.** Changes in the clinical parameters during hospitalization in 6 patients with giant cell myocarditis. Echocardiography data for (A) left ventricular ejection fraction (LVEF) and (B) LV end-diastolic dimension (LVDd). Serum levels of (C) B-type natriuretic peptide (BNP) and (D) troponin T. The solid lines indicate the change in the parameters in patients 4 and 6, the dotted lines for patient 1, and the dashed lines for patients 2, 3 and 5 who received a ventricular assist device.
output syndrome or subsequent sepsis. The autopsy results of patient 3 showed severe myocardial replacement fibrosis with lymphocytic infiltration, without apparent infiltration of giant cells.

Patients 4 and 6 did not require VAD or re-implantation of MCS and were discharged home. They survived for >1 year after p-MCS discontinuation, with preservation of cardiac function (LVEF of 54% and 58%, respectively, and LVdL of 48 mm and 47 mm, respectively).

With regard to adverse events, an infection developed during device support in 2 of the 6 patients: patient 2 developed mediastinitis and patient 5 developed prostatis and septic shock caused by a catheter-related bloodstream infection. There were no incidents of device-related infection.

**Discussion**

We reviewed the clinical and disease outcomes for 6 patients with fulminant GCM, and report poor outcomes for patients requiring pVAD treatment. Previous research has reported an extremely poor prognosis for patients with GCM, with a mean survival period of 3 months when immunosuppressive therapy is not used. In recent years, immunosuppressants, and CyA principally, have been widely used as a component of the treatment of GCM, with evidence of improvement in the HTx-free survival rate. However, evidence of outcomes in patients with GCM requiring MCS support is limited to small case series studies, with the immunosuppressant regimen used in those cases not having been fully clarified. Although treatment of GCM without immunosuppressive therapy or a single immunosuppressant course of steroids has often been accepted, the HTx-free survival in these cases is very low. Of note, a few studies have reported favorable outcomes in patients with fulminant GCM requiring MCS support when treated early with an aggressive immunosuppressant protocol. In our case series, single steroid immunosuppressive therapy was used in patients 1, 2, and 3 to prevent device-related infection; however, the clinical course of these patients was not favorable. Based on these outcomes, we currently use a standard immunosuppressant regimen of a combination of steroid and CyA for the treatment of GCM, even under MCS support. This may be because in all patients, the device support was continued.

Of note, the 2017 data from the United Network for Organ Sharing Registry, the 10-year survival rate after HTx for patients with GCM is 68%, which is not different to the rate for any other disease requiring HTx. Although 6–25% of all patients with GCM experience disease relapse after HTx, the response of these patients to immunosuppressive therapy is generally good. In our case series, patients who were weaned off LVAD despite incomplete recovery of cardiac function had a poor prognosis. With future approvals of DT, it may be possible that patients with GCM might be able to receive long-term circulatory support using an implantable LVAD to further improve their long-term prognosis. Even in such cases, immunosuppressive therapy should be continued to maintain cardiac function, especially the function of the right heart on VAD support.

In our case series, there was no incidence of device-related infection after the initiation of immunosuppressive therapy, although some patients did develop systemic infections. This may be because in all patients, the device support period did not extend beyond 78 days, regardless of the type of mechanical system used to support cardiac function. It is possible that device-related infection might pose a problem if a long-term implantable LVAD is used, which will need to be considered. Biopsy-guided adjustment of the intensity of immunosuppressive therapy can lower the risk of device-related infection, as well as other opportunistic infections. It is possible that, in the future, indications for HTx in patients with GCM could be re-evaluated after confirming patient prognosis after long-term LVAD support using DT.
The limitations of our case series need to be acknowledged. First, the number of patients with GCM in Japan is relatively low compared with Western countries, even if our institution is one of the high-volume centers for heart failure treatment in Japan. Therefore, we cannot conclude that a particular treatment strategy is correct from our case series; more precise investigations, using data from multicenter databases, are warranted to clarify the most effective treatment approach for GCM. Second, due to the mandate of our institution, less severe cases of GCM are not referred to our institution and, as such, the patients evaluated in our study may not accurately represent the range of characteristics of patients with GCM.

Conclusions
The rate of MCS use in patients with GCM is high, and patient prognosis is poor. In particular, patients who ultimately require VAD often do not achieve long-term survival in Japan, where HTx candidacy for GCM cannot be easily obtained and DT has not been approved. A therapeutic strategy that combines MCS and early administration of CyA-based multiple immunosuppressive therapies will be useful.

Disclosures
The authors declare that they have no conflicts of interest.

References