Successful Triple Combination Immunosuppressive Therapy with Prednisolone, Cyclosporine, and Mycophenolate Mofetil to Treat Recurrent Giant Cell Myocarditis

Akita, Tomomi ; Mori, Shumpei ; Onishi, Akira ; Hara, Shigeo ; Yamada, Haruhi ; Nagasawa, Akira ; Imada, Hiroshi ; Shimoura, Hiroyuki ; Ooka,…

(Citation)
Internal Medicine,58(14):2035-2039

(Issue Date)
2019-07-15

(Resource Type)
journal article

(Version)
Version of Record

Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2471-18
Intern Med 58: 2035-2039, 2019
http://internmed.jp

【 CASE REPORT 】

Successful Triple Combination Immunosuppressive Therapy with Prednisolone, Cyclosporine, and Mycophenolate Mofetil to Treat Recurrent Giant Cell Myocarditis

Tomomi Akita[1], Shumpei Mori[1], Akira Onishi[2], Shigeo Hara[3], Haruhi Yamada[1], Akira Nagasawa[1], Hiroshi Imada[1], Hiroyuki Shimoura[1], Junichi Ooka[1], Hidekazu Tanaka[1] and Ken-ichi Hirata[1]

Abstract:
A 59-year-old man with a history of giant cell myocarditis was admitted to our hospital with recurrent giant cell myocarditis triggered by a 1 mg/day taper in his prednisolone dose. During the initial episode, he had undergone rescue implantation of a temporary left ventricular assist device followed by the administration of dual immunosuppressive therapy with prednisolone and concomitant cyclosporine. Triple combination immunosuppressive therapy maintained with additional mycophenolate mofetil successfully controlled recurrent myocarditis, enabled a reduction in the prednisolone dose, and achieved the functional recovery of the left ventricle.

Key words: cyclosporine, giant cell myocarditis, mycophenolate mofetil, prednisolone, recurrence

(Intern Med 58: 2035-2039, 2019)
(DOI: 10.2169/internalmedicine.2471-18)

Introduction

Historically, giant cell myocarditis is a fulminant and fatal form of myocarditis commonly associated with progressive congestive heart failure, refractory ventricular arrhythmias, and cardiogenic shock, and consequently an unfavorable prognosis (1, 2). Approximately 20% of all cases are associated with autoimmune disorders, including inflammatory bowel disease (8%), as well as thyroiditis, and thymoma (1, 2). Previous studies have shown that combination immunosuppressive therapy improves survival (3-5); however, the tapering or withdrawal of immunosuppressants is associated with a lifelong risk of recurrence affecting the native heart (2, 4, 5). To date, no optimal regimen and duration of immunosuppressive therapy have yet been established to prevent or treat recurrent giant cell myocarditis. We herein report a case of recurrent giant cell myocarditis that was successfully treated with triple combination therapy.

Case Report

A 58-year-old man with a history of ulcerative colitis was transferred to our hospital with cardiogenic shock for which he had been treated with catecholamines, intra-aortic balloon pumping, percutaneous cardiopulmonary support, and mechanical ventilation. He had a recent history of generalized myalgia, muscle weakness, and diplopia. A significant elevation in the muscular, as well as cardiac enzyme levels were observed. Based on these specific clinical features, electromyographic findings (myogenic changes), and magnetic resonance imaging findings (hyperintense signal in the extraocular muscle on T2-weighted images), he was diagnosed with polymyositis (including extraocular myositis as the cause of diplopia). An endomyocardial biopsy performed on the day of admission confirmed CD3+ T-lymphocyte (pre-

[1]Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan, [2]Department of Rheumatology and Clinical Immunology, Kobe University Graduate School of Medicine, Japan and [3]Department of Diagnostic Pathology, Kobe City Medical Center General Hospital, Japan
Received: December 3, 2018; Accepted: January 10, 2019; Advance Publication by J-STAGE: March 28, 2019
Correspondence to Dr. Shumpei Mori, shumpei_8@hotmail.com

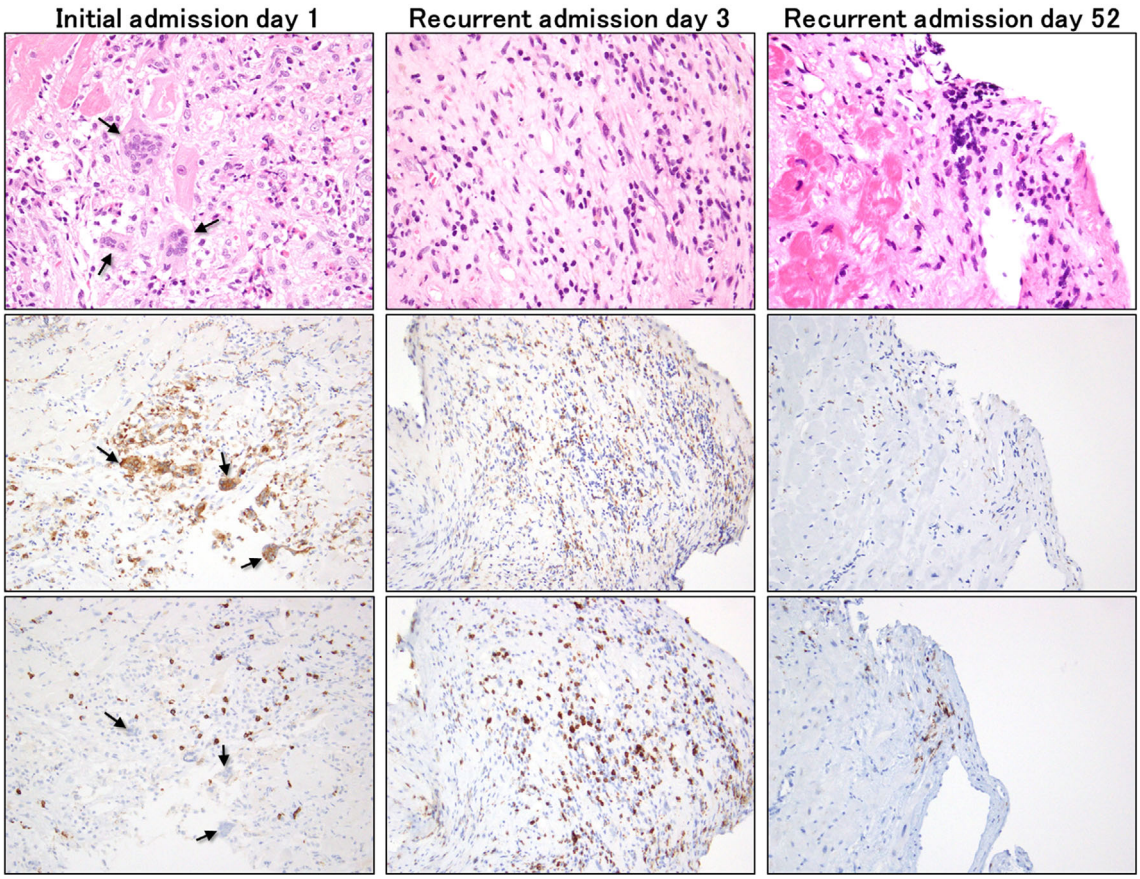

Figure 1. **Histopathological findings of serial endomyocardial biopsies. A Hematoxylin and Eosin staining image (upper panel) using 400× magnification shows inflammation with myocardial shedding and interstitial fibrosis. Giant cells (black arrows) are confirmed only in the initial specimen obtained upon admission (left panel). Immunostaining performed using 200× magnification shows infiltration of CD68+histiocytes (mid-line panel) and CD8+T-lymphocytes (lower panel). It should be noted that the giant cells are CD68 positive. The right panel shows the findings of the endomyocardial biopsy repeated on day 52 of admission. Inflammation is observed to have subsided in this specimen compared with that observed in the biopsy obtained on day 3 of admission (middle panel). However, smoldering inflammation is observed in this specimen, which necessitated the addition of mycophenolate mofetil to the combined regimen of prednisolone and cyclosporine.**

dominantly CD8+ vs. CD4+) and CD68+ multinucleated giant cell infiltration (Fig. 1). Although myocardial infiltration of the multinucleated giant cells is also a characteristic pathological finding in cardiac sarcoidosis, no clinical or laboratory findings suggesting cardiac, lung, skin, or ocular sarcoidosis were detected in this case. Accordingly, following the diagnosis of fulminant giant cell myocarditis associated with polymyositis, he was treated with 9-day rescue implantation of a left ventricular assist device, 3-day methylprednisolone pulse therapy, and intravenous immunoglobulin therapy, followed by maintenance immunosuppressive therapy with prednisolone (50 mg/day) and cyclosporine (150 mg/day). During this initial clinical course, his peak brain natriuretic peptide and troponin I levels increased to 809 pg/mL and 27.5 ng/mL, respectively. He recovered completely after 3 months of hospitalization without any neurological and/or physical deficit and was discharged with prednisolone 20 mg/day and cyclosporine 100 mg/day. The left ventricular ejection fraction improved rapidly from 6% to 51% on day 21 and to 68% on day 50 with a reduction in serum cardiac troponin I levels to <0.1 ng/mL (6).

A month after discharge, his oral prednisolone was reduced from 20 mg/day to 19 mg/day. However, 16 days after this 1 mg/day dose reduction, he was re-admitted with cardiogenic shock. During re-hospitalization, his left ventricular ejection fraction had worsened to 15%. Clinically, he showed no evidence of worsened polymyositis. The serum brain natriuretic peptide and troponin I levels showed a re-elevation to 3,781 pg/mL and 0.66 ng/mL, respectively. He was promptly administered catecholamine and received intra-aortic balloon pumping followed by 3-day methylprednisolone pulse therapy and intravenous immunoglobulin therapy. The prednisolone dose was again increased to 60 mg/day with a maintenance dose of continuous cyclosporine at 100 mg/day. An endomyocardial biopsy performed on day 3 showed active myocarditis with myocardial shedding, interstitial fibrosis, and CD3+ T-lymphocyte (predominantly CD8+ vs. CD4+) and CD68+ histiocyte infiltration. Al-

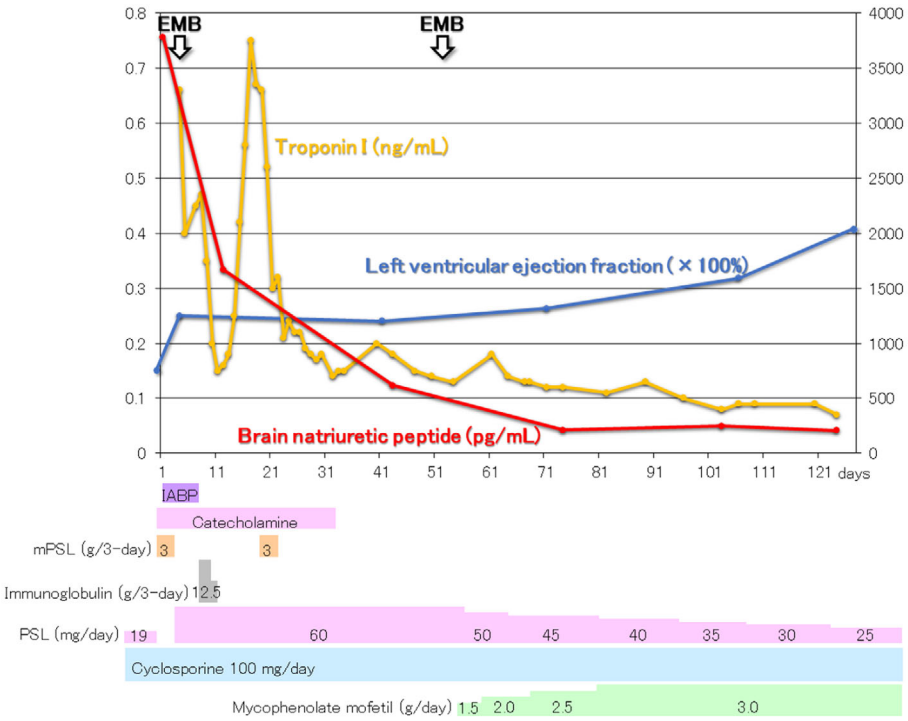

Figure 2. **The patient's clinical course during his second admission. After the administration of mycophenolate mofetil, the serum troponin I levels decreased gradually along with a gradual improvement in the left ventricular ejection fraction. EMB: endomyocardial biopsy, IABP: intra-aortic balloon pumping, mPSL: methylprednisolone, PSL: prednisolone**

though multinucleated giant cells could not be identified in the histopathological specimens, he was clinically diagnosed with recurrent giant cell myocarditis (Fig. 1). Fortunately, his hemodynamic status gradually improved without left ventricular assist device implantation. The left ventricular ejection fraction improved to 25% on day 5, and intra-aortic balloon pumping could be discontinued on day 8. Although his serum troponin I level decreased to 0.15 ng/mL on day 14, it again increased to 0.75 ng/mL on day 17 without any significantly worsened hemodynamics. Additional 3-day methylprednisolone pulse therapy was administered, which reduced his serum troponin I level to 0.1-0.2 ng/mL. The serum C-reactive protein level also decreased to <0.01 mg/dL over time. He was transferred to the general ward on day 32 without catecholamine support. Although the peak serum troponin I level was lower and hemodynamic impairment was milder during his second admission than that during his initial presentation, the left ventricular ejection fraction recovery was poorer as evidenced by a left ventricular ejection fraction of 24% on day 40 with persistently elevated serum troponin I levels of approximately 0.1-0.2 ng/mL. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography performed on day 45 showed no specific accumulation involving the heart as well as other organs. Based on these mixed findings, we did not reduce the dose of prednisolone below 60 mg/day. Finally, an endomyocardial biopsy repeated on day 52 confirmed an improved, but smoldering inflammation with myocardial shedding, interstitial fibrosis, and residual CD3+ T-lymphocyte (predominantly CD8+ vs. CD4+) and CD68+ histiocyte infiltration without giant cells (Fig. 1). Considering the glucocorticoid/cyclosporine-resistant smoldering inflammation, mycophenolate mofetil (1.5 g/day) was added to his regimen on day 53 with a gradual increase in dose to 3.0 g/day as replacement therapy for the gradual prednisolone taper from 60 mg/day to 40 mg/day over the subsequent 3 weeks. Fortunately, the serum troponin I levels showed a gradual reduction to <0.1 ng/mL along with a gradual improvement in left ventricular ejection fraction to 32% on day 106 (Fig. 2). Eventually, he was discharged 4 months after re-hospitalization with triple combination immunosuppressive therapy including prednisolone 25 mg/day, cyclosporine 100 mg/day, and mycophenolate mofetil 3.0 g/day in addition to the standard regimen prescribed for the management of heart failure with a reduced ejection fraction (perindopril 2 mg/day, bisoprolol 2.5 mg/day, and eplerenone 12.5 mg/day). His clinical course which had been monitored as an outpatient has been uneventful, and the patient is asymptomatic 25 months after his discharge following re-hospitalization. Ventricular arrhythmia had not been observed throughout the clinical course. The serum brain natriuretic peptide and troponin I levels have been maintained at approximately 100 pg/mL and 0.01-0.02 ng/mL, respectively, with the administration of prednisolone 11 mg/day, cyclosporine 100 mg/day, and mycophenolate mofetil 3.0 g/day. The left ventricular ejection fraction has further improved to 45%.

Discussion

Giant-cell myocarditis is a rapidly progressive myocardial disease of unknown pathogenesis, presumably mediated by T-lymphocytes and anti-myosin autoantibodies (2). Histopathological examinations reveal multifocal or diffuse infiltration of predominantly CD8+ T-lymphocytes, eosinophils, and multinucleated giant cells (7). Previous reports have shown that contemporary immunosuppression with the administration of cyclosporine and corticosteroids improved the prognosis, and approximately two-thirds of such patients achieved a partial clinical remission characterized by recovery from severe heart failure without the need for transplantation (4), compared with a mean 3-month survival period in patients who did not receive immunosuppressants (1). Recurrent giant cell myocarditis has been observed in 12% of cases, following a decrease in the dose or withdrawal of immunosuppressants even up to 8 years after the initial diagnosis (2, 5). The 5-year transplantation-, recurrence-, heart failure-, and ventricular arrhythmia-free survival rate was 35% (5).

Thus, as shown in the present case, giant cell myocarditis is a chronic condition with a high risk of recurrence in the native heart (8). To date, no optimal treatment regimen or duration of immunosuppressive therapy has been conclusively established even as primary treatment, even more so in patients with recurrence. Dual therapy with cyclosporine and corticosteroids or triple therapy with cyclosporine, azathioprine, and corticosteroids may prolong survival when promptly initiated at the time of diagnosis or in patients with a suspected diagnosis (7). Alternative immunosuppressive regimens, including the use of proliferation signal inhibitors, mycophenolate mofetil, tacrolimus, sirolimus, methotrexate, and anti-thymocyte globulin have been reported (7-9). Based on the possible pathogenesis, therapy targeting T-lymphocytes and anti-myosin autoantibodies appears to be effective in successfully treating giant cell myocarditis, particularly in combined regimens.

After oral administration and absorption, mycophenolate mofetil is rapidly hydrolyzed to yield mycophenolic acid, an active immunosuppressive agent. Mycophenolic acid is a relatively selective antimetabolite, which exerts a potent and reversible inhibition of the inosine monophosphate dehydrogenase level (rate-limiting enzyme in the de novo pathway for purine synthesis and proliferation of lymphocytes) expressed in stimulated lymphocytes. *In vitro*, mycophenolate mofetil blocks the proliferation of both B- and T-lymphocytes, inhibits antibody formation and the generation of cytotoxic T-lymphocytes, and decreases the expression of adhesion molecules, thus impairing the ability of lymphocytes to bind to endothelial cells (10). Mycophenolate mofetil is widely used as a standard and first-line component of several different immunosuppressive regimens, particularly in the field of solid organ transplantation (11) and in patients with lupus nephritis (12). Azathioprine is a useful alternative; however, it was not considered in this particular case owing to liver dysfunction observed in the patient at the time.

Giant cell myocarditis is diagnosed based on endomyocardial biopsy findings. The biopsy should be performed during the acute phase of the disease to enable the prompt initiation of immunosuppressive therapy. In this case, the sensitivity of the first endomyocardial biopsy performed at the time of diagnosis was relatively low at 68% and subsequently increased to 93% by the time the third biopsy was performed. Thus, an accurate diagnosis of giant cell myocarditis often requires repeat endomyocardial biopsies (4). A diagnosis based on endomyocardial biopsy may be inaccurate, particularly in patients with a recurrence of giant cell myocarditis in the native heart, as was observed in the present case (giant cells were not identified even in the repeat biopsy specimens). In patients receiving immunosuppressants, giant cells tend to disappear early during the disease process, and the inflammatory manifestation that disappears last is smoldering lymphocytic myocarditis, which is followed by replacement-type interstitial fibrosis (5). In cases of recurrence, therefore, the giant cell number did not affect immunosuppressive regimen (5). Thus, immunosuppressive therapy should be restarted or switched to more aggressive regimens in patients with a high index of suspicion for recurrent giant cell myocarditis. As was confirmed in the present case, the detection of CD68+ histiocytes may indicate that a similar pathogenetic mechanism is involved in those with recurrence (based on the presumption that histiocytes are possible precursors of CD68+ giant cells). The serum troponin I levels (which indicate latent and smoldering myocarditis) therefore need to be closely and regularly monitored.

In conclusion, our case highlights the efficacy of adding mycophenolate mofetil to a combined regimen of prednisolone and cyclosporine to treat patients with recurrent giant cell myocarditis. This regimen could control the smoldering myocardial inflammation, achieve a reduction in the prednisolone dose, and thus lead to the functional recovery of the left ventricle.

The authors state that they have no Conflict of Interest (COI).

References

1. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis-natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med **336**: 1860-1866, 1997.
2. Cooper LT Jr, ElAmm C. Giant cell myocarditis. Diagnosis and treatment. Herz **37**: 632-636, 2012.
3. Cooper LT Jr, Hare JM, Tazelaar HD, et al. Giant Cell Myocarditis Treatment Trial Investigators. Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol **102**: 1535-1539, 2008.
4. Kandolin R, Lehtonen J, Salmenkivi K, Räisänen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ

Heart Fail **6**: 15-22, 2013.

5. Maleszewski JJ, Orellana VM, Hodge DO, Kuhl U, Schultheiss HP, Cooper LT. Long-term risk of recurrence, morbidity and mortality in giant cell myocarditis. Am J Cardiol **115**: 1733-1738, 2015.

6. Ooka J, Tanaka H, Hatani Y, et al. Treatment of fulminant giant cell myocarditis associated with polymyositis using a left ventricular assist device and subsequent corticosteroid and immunosuppressive therapy leading to remission. Intern Med **56**: 2155-2158, 2017.

7. Shih JA, Shih JA. Small steps for idiopathic giant cell myocarditis. Curr Heart Fail Rep **12**: 263-268, 2015.

8. Yeen WC, Haas G, Mehmood SA, Crestanello JA. Relapse of giant cell myocarditis supported with veno-arterial extracorporeal membrane oxygenation. Interact Cardiovasc Thorac Surg **12**: 829-831, 2011.

9. Fluschnik N, Escher F, Blankenberg S, Westermann D. Fatal recurrence of fulminant giant cell myocarditis and recovery after initialisation of an alternative immunosuppressive regime. BMJ Case Rep **2014**: bcr2014206386, 2014.

10. Remuzzi G, Cravedi P, Costantini M, et al. Mycophenolate mofetil versus azathioprine for prevention of chronic allograft dysfunction in renal transplantation: the MYSS follow-up randomized, controlled clinical trial. J Am Soc Nephrol **18**: 1973-1985, 2007.

11. van Gelder T, Hesselink DA. Mycophenolate revisited. Transpl Int **28**: 508-515, 2015.

12. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med **353**: 2219-2228, 2005.