Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3322-19
Intern Med 59: 113-118, 2020
http://internmed.jp

【 CASE REPORT 】

Myocarditis with Advanced Atrioventricular Block after Allogeneic Stem Cell Transplantation: A Case Report and Literature Review

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Abstract:
A 51-year-old woman with Philadelphia chromosome-positive acute lymphoblastic leukemia underwent a second cord blood transplantation followed by maintenance therapy with interferon-α. After 33 months, she developed cardiogenic shock caused by advanced atrioventricular block. Laboratory tests revealed increased myocardium enzymes, and ultrasonic cardiography demonstrated mild thickening of the left ventricular wall. She was diagnosed with myocarditis and successfully treated using prednisolone. Myocarditis after allogeneic stem cell transplantation is a rare but potentially fatal complication. However, it is important for physicians to be aware of this complication because all of the symptoms may be reversed with immunosuppressive treatment.

Key words: myocarditis, atrioventricular block, allogeneic stem cell transplantation, graft-versus-host disease

(Intern Med 59: 113-118, 2020)
(DOI: 10.2169/internalmedicine.3322-19)

Introduction

Myocarditis, an inflammatory disease of the heart frequently resulting from viral infections or immune-mediated response (1, 2), is a rare but potentially fatal complication in allogeneic stem cell transplantation (allo-SCT) recipients. Some patients with myocarditis who were successfully treated by immunosuppressive therapy have been reported (3-7). However, allo-SCT recipients have multiple factors that may lead to myocarditis, including a high risk of viral infection and allogeneic immune reactions. Therefore, the management of myocarditis in allo-SCT recipients is thought to be more complicated and difficult than in non-transplant patients (8).

In 2017, we reported a second cord blood transplantation (CBT) followed by maintenance therapy with interferon-α (IFN-α) for a patient with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) with a T315I mutation after unrelated bone marrow transplant (BMT) (9). This patient has maintained molecular complete remission (CR) for more than five years. However, 33 months after the initiation of IFN-α therapy, she developed myocarditis.

Case Report

A 51-year-old woman was diagnosed with Ph^+ ALL in December 2012. She received three courses of hyper-CVAD and one course of high-dose methotrexate and cytarabine concurrent with dasatinib (10). BMT from an unrelated donor was performed in May 2013. The first allo-SCT conditioning regimen consisted of cyclophosphamide (120 mg/kg) and total body irradiation (TBI; 12 Gy). However, hematological relapse with the T315I mutation in the BCR-ABL gene was confirmed by a bone marrow examination in August 2013, and she received one course of hyper-CVAD. In October 2013, the patient underwent a second CBT and suc-

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Received: May 10, 2019; Accepted: July 9, 2019; Advance Publication by J-STAGE: August 28, 2019
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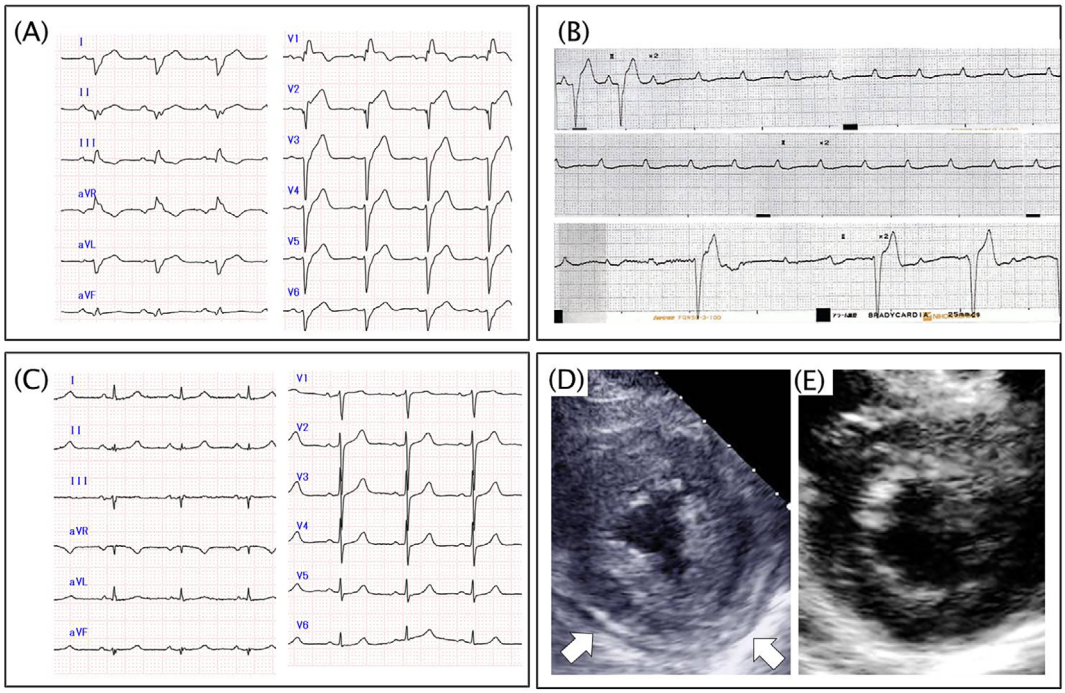

Figure 1. **(A) Electrocardiography (ECG) at admission showed sinus rhythm with complete right bundle branch block. (B) ECG at 4 hours after admission showed advanced atrioventricular block with a long pause (maximum: 40 seconds) of the QRS complex. (C) Follow-up ECG two months after the onset was normal. (D) Ultrasonic cardiography (UCG) at 4 hours after admission revealed mild thickening of the left ventricular wall and slight pericardial effusion (white arrows). (E) Follow-up UCG on the 25th day revealed normalization of the wall thickness and disappearance of the pericardial effusion.**

cessfully achieved molecular CR again. The second allo-SCT conditioning regimen consisted of fludarabine at 125 mg/m^2, melphalan at 80 mg/m^2, and TBI of 4 Gy. The total cumulative dose of doxorubicin was 200 mg/m^2. The immunosuppressive agents were successfully tapered off by January 2014. At that time, the patient had moderate chronic graft-versus-host disease (GVHD). However, considering the markedly high risk of relapse, we started maintenance therapy with IFN-α. The patient provided her written informed consent, and the use of IFN-α was approved by our institutional review board.

In December 2016, the patient was admitted after faintness and vomiting. Her blood pressure (BP) was 78/56 mmHg, heart rate was 102 beats per minute, body temperature was 36.9℃, and oxygen saturation according to pulse oximetry was 96%. At that time, the patient did not exhibit deterioration in chronic GVHD. The laboratory tests revealed increased myocardium enzyme levels: creatinine kinase (CK) of 886 U/L (normal range 30-170 U/L), CK-MB of 27.3 U/L (normal range <5 U/L), troponin-T of 4.1 ng/mL (normal range <0.0029 ng/mL), lactic dehydrogenase of 448 U/L (normal range 110-220 U/L), and aspartate transaminase of 192 U/L (normal range 10-30 U/L). Electrocardiography (ECG) demonstrated sinus rhythm with complete right bundle branch block (Fig. 1A). Mild thickening of the left ventricular wall, slight pericardial effusion, and a normal ejection fraction were observed on transthoracic ultrasonic cardiography (UCG) (Fig. 1D). Four hours after admission, the patient developed syncope, and advanced atrioventricular block with long pause (maximum: 40 seconds) of the QRS complex was noted on ECG (Fig. 1B). The patient received temporary cardiac pacing and dopamine to maintain her BP. No coronary stenosis was found on coronary angiography to explain the increased myocardium enzyme levels. A tentative diagnosis of myocarditis was made, and IFN-α was discontinued.

As we were unable to specify the etiology of myocarditis, we administered supportive therapy, including antimicrobials, parenteral nutrition, diuretics, dopamine, and oxygenation. However, in the 48 hours following her admission, her BP gradually decreased despite cardiac pacing and dopamine administration. Two days after her admission, the patient developed respiratory distress and hypoxemia, and bilateral infiltrate was observed on chest X-ray; therefore, she was diagnosed with congestive heart failure. The serum CK (CK-MB) level had increased to 1,207 (61.8) U/L. The presumed diagnosis was myocarditis associated with allogeneic immune reaction.

The patient was immediately treated using 1 mg/kg/day of prednisolone. After the initiation of corticosteroid therapy following the gradual improvement in hemodynamics, the myocardium enzyme levels decreased. Dopamine was successfully tapered off on the seventh day. To confirm myocarditis, an endomyocardial biopsy (EMB) was performed

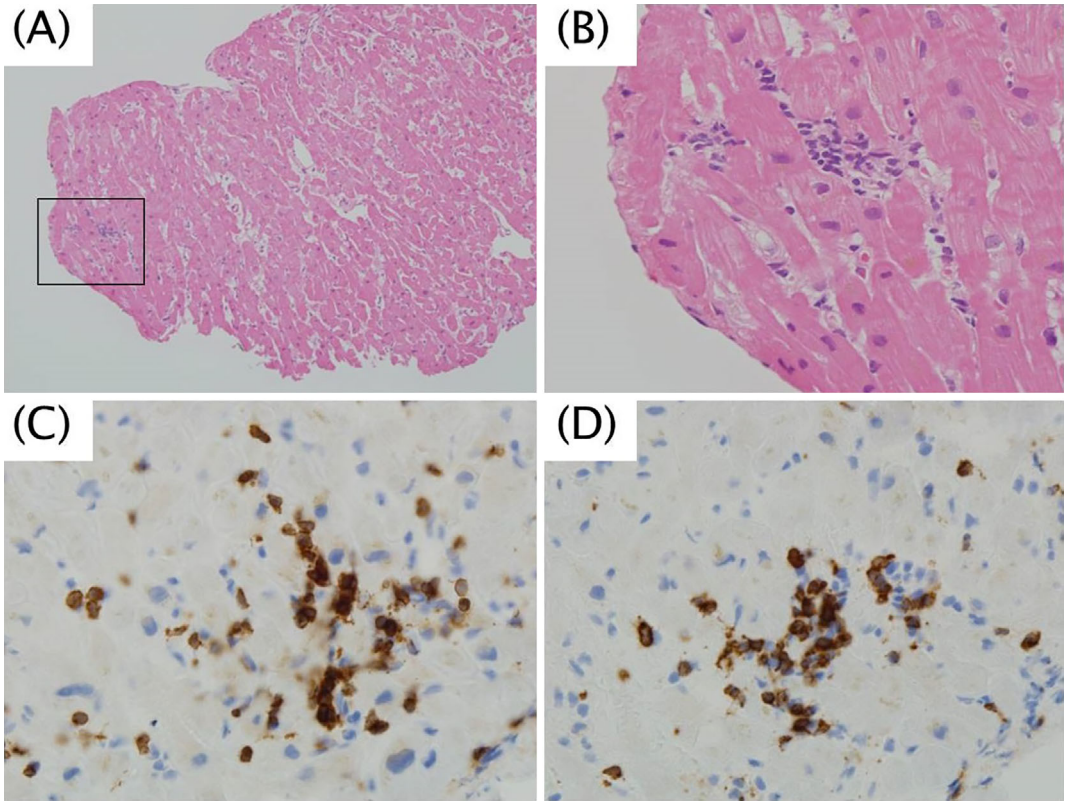

Figure 2. **(A) Cross-section of a myocardium biopsy sample at 9 days after admission [Hematoxylin and Eosin (H&E) staining ×100]. (B) Magnified images of the areas indicated by the squares in panel A demonstrate infiltration of lymphocytes (H&E staining ×400). (C, D) The infiltrating lymphocytes were positive for CD3 (C) and CD8 (D) (×400).**

on the ninth day. Although the biopsy sample was obtained after the initiation of corticosteroid therapy, CD8+ T-cell infiltration within the myocardium was confirmed by a pathological examination (Fig. 2). Follow-up UCG on the 25th day revealed normalization of the wall thickness and disappearance of the pericardial effusion (Fig. 1E). Follow-up ECG two months after the onset showed normal findings (Fig. 1C). Prednisolone was tapered starting on the seventh day and successfully stopped by 12 months after the onset without recurrence of myocarditis or deterioration of chronic GVHD. We evaluated the antibody titers against coxsackievirus type B1, B2, B3, B4, B5, and B6 at admission and at the 24-month follow-up. Her antibody titer against coxsackievirus type B6 at the 24-month follow-up was slightly higher (×4) than that at admission (<×4). The clinical course after the onset of myocarditis is summarized in Fig. 3.

Discussion

Myocarditis is an inflammatory disease of the myocardium caused by infectious or noninfectious triggers (1, 2). The majority of myocarditis cases are thought to result from common viral infections and post-viral immune-mediated reactions. In patients with viral myocarditis, the initial change is myocyte damage in the absence of a cellular immune response (1, 2). Following the initial damage, myocyte injury may be mediated through activated immune responses. In addition to viral infections, some myocarditis patients have autoimmune etiologies, such as giant cell myocarditis or hypersensitivity myocarditis (1, 2). In viral myocarditis, the most commonly cited viruses are enteroviruses, especially coxsackievirus, adenovirus, parvovirus B12, human herpesvirus 6, cytomegalovirus, and Epstein Barr virus (1, 2). Nakaseko et al. reported an allo-SCT recipient with presumable viral fulminant myocarditis who was diagnosed by an antibody study for cardiotropic viruses (11). In our patient, the follow-up antibody titer against coxsackievirus type B6 was slightly higher than that at admission. However, we did not examine antibody titers during the recovery phase (four to eight weeks). Therefore, the higher antibody titer may have resulted from asymptomatic or undifferentiated febrile coxsackievirus infection that was unrelated to the myocarditis.

Although the utility of virus serology for patients with suspected myocarditis remains unclear, Mahfoud et al. reported viral serological evidence of infection for the same virus detected by nested polymerase chain reaction (PCR) in EMB in 5 of 124 patients (4%) (12). Furthermore, in allo-SCT recipients, serological assays may be of limited value in diagnosing viral infection due to the immunocompromised status resulting in a reduction of the total antibody

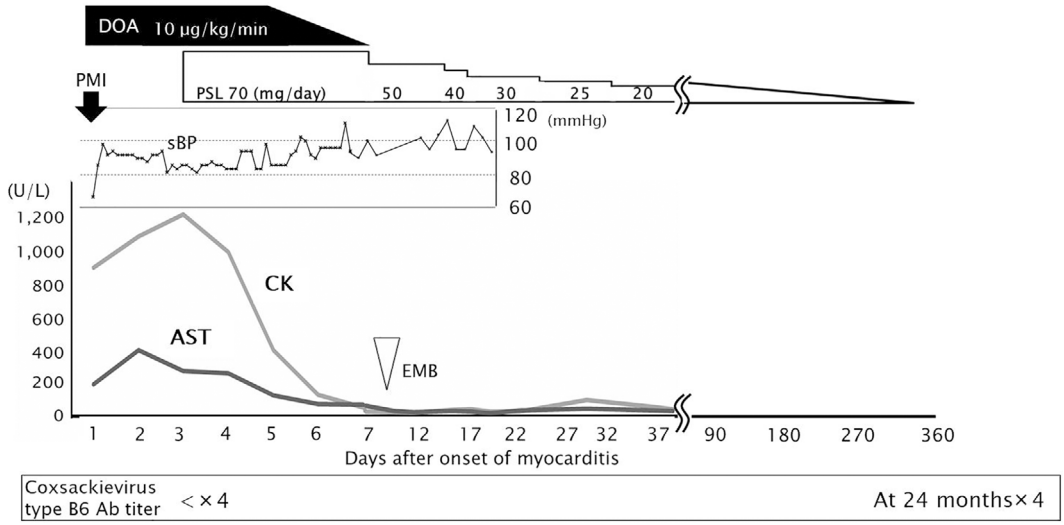

Figure 3. Clinical course after the onset of myocarditis. DOA: dopamine, PSL: prednisolone, PMI: pacemaker implantation, sBP: systolic blood pressure, CK: creatinine kinase, AST: aspartate transaminase, EMB: endomyocardial biopsy, Ab: antibody

amount. Therefore, direct viral detection by molecular biology-based techniques may be more important for allo-SCT recipients than other approaches.

We performed EMB 9 days after admission, but as the PCR assay for the causative virus is not yet approved in Japan, we were unable to perform a PCR assay for the EMB sample to elucidate the etiology of the myocarditis. However, regardless of the etiology of her myocarditis, the persistence of CD8+ T-cell infiltration within the myocardium even after the initiation of corticosteroid therapy suggested that donor-derived immunological systems played an important role in her myocarditis.

In the field of allo-SCT, only 10 cases, including ours, of myocarditis associated with allogeneic immune reactions have been reported. Details of the cardiac manifestations and GVHD history are provided in Table (3-7, 13-16). The time from HSCT to the onset of myocarditis varied, and the median was 109 days (range, 8-1,173 days). UCG findings were reported in seven cases, and a significant reduction in the ejection fraction was reported in four cases. Pericardial effusion was observed in four cases. Pathological findings were reported in six cases, and infiltration of CD8+ T-cells was evident in five cases. Although three of the patients died suddenly, six were rescued by immunosuppressive therapy. These findings suggest that the heart is a target of alloreactive T-cells after allo-SCT. In myocarditis associated with allogeneic immune reactions, some patients may have a poor prognosis, including sudden cardiac death, but the response to immunosuppressive therapy may be generally good.

Rackley et al. reported 11 patients with cardiac manifestations associated with GVHD (15). Only one male patient (Table, case 5) suffered myocarditis with sudden death 7.5 months after allo-SCT. In contrast, 8 patients had bradyarrhythmia associated with GVHD, which was responsive to increased immunosuppression, but clinical data, including ECG, UCG, and myocardium enzyme levels at the onset, were not detailed in the report. In general, the clinical manifestations of myocarditis are highly variable, ranging from subclinical disease to fatigue, cardiogenic shock, and sudden death (1, 2). Therefore, some of the eight patients may have had subclinical myocarditis. The major symptom of myocarditis exhibited by our patient was syncope caused by advanced atrioventricular block, which responded well to corticosteroid therapy. Bradyarrythmia may be a clinical characteristic of cardiac GVHD complicated by myocarditis after allo-SCT.

In cases of coxsackievirus B3-induced myocarditis, IFN-β and IFN-α_2 therapy protect myocytes against injury (17). However, Sacchi et al. reported 4 patients with new cardiomyopathy among 588 patients with immune-mediated and unusual complications associated with IFN-α therapy for chronic myelogenous leukemia (18). In our patient, to enhance the graft-versus-leukemia effects, we performed IFN-α maintenance therapy following the second CBT (9). The IFN-α therapy may have helped eradicate the causative virus from the myocardium and increased myocyte injury due to the adaptive immune response. In fields other than allo-SCT, immunosuppressive agent treatment for acute myocarditis has shown controversial results. Chen et al. reported that corticosteroids do not reduce the mortality for patients diagnosed with viral myocarditis (19). However, Frustaci et al. evaluated the efficacy of immunosuppression for virus-negative inflammatory cardiomyopathy in a randomized placebo-controlled study and found that 88% of the virus-negative inflammatory cardiomyopathy patients exhibited an improved cardiac function after immunosuppressive therapy (20). Immunosuppressive therapy, including corticosteroids, may be an effective and promising strategy for controlling excessively activated donor-derived immunological reac-

Table. Reports of Recipients with Myocarditis Associated with Allogeneic Immune Reactions.

No	age/sex	GVHD	Onset day	ECG findings	UCG findings	CK (U/L)	Therapy	Pathology	Outcome	Days from the onset to the outcome	Reference No.
1	8 w/F	(+)	27	Heart block.	NA	NA	PMI, ALG	Lymphoid and histiocytic infiltration, focal necrosis.	Died	10	13
2	4 m/M	(+)	8	Complete AV block.	EF40%	NA	Corticosteroid, CsA	NA	Improved	7	3
3	17 y/M	(+)	15	Sinus tachycardia, low voltage, sudden death	Diffuse hypokinesis EF30%, small pericardial effusion.	NA	Corticosteroid, CsA	Cytolysis and massive infiltration of CD8+T-cells.	Died	1	14
4	29 y/M	(+)	43	NA	LV wall thickening, starry sky, pericardial effusion, EF61%.	NA	Corticosteroid	NA	Improved	21	4
5	18 y/NA	(+)	225	Sudden death	NA	NA	(-)	NA	Died	1	15
6	9 y/M	(+)	270	Ventricular fibrillation, sudden death	NA	559	(-)	Giant cell myocarditis, CD8+T-cells.	Died	1	16
7	18 y/F	(+)	193 (post DLI 102 days)	Sinus tachycardia, IRBBB, ST-T change.	Mild hypokinesia of the left interventricular septal wall.	8,872	Corticosteroid, Tac	Infiltration of CD8+T-cells.	Improved	14	5
8	50 y/F	(+)	143	Sinus tachycardia, IRBBB, ST-T change.	Diffuse hypokinesis, pericardial effusion EF32%.	2,027	Corticosteroid, Tac	NA	Improved	14	6
9	15 y/F	(-)	75	Widened QRS with ST and T wave abnormality.	Diffuse hypokinesis EF27%.	NA	Mechanical support, corticosteroid, IVIG	Infiltration of CD8+T-cells.	Improved	17	7
P/C	56 y/F	(+)	1,173	CRBBB, ST-T change, advanced AV block.	Diffuse LV wall thickening, pericardial effusion, EF75%.	886	PMI, corticosteroid	Infiltration of CD8+T-cells.	Improved	7	

GVHD: graft versus host disease, ECG: electrocardiography, UCG: ultrasonic cardiography, CK: creatinine kinase, M: male, F: female, NA: not available, y: years, m: months, w: weeks, DLI: donor lymphocyte infusion, AV: atrioventricular, IRBBB: incomplete right bundle branch block, CRBBB: complete right bundle branch block, EF: ejection fraction, LV: left ventricle, PMI: pacemaker implantation, ALG: antilymphocyte globulin, CsA: cyclosporine A, Tac: tacrolimus, IVIG: intravenous immunoglobulin, P/C: present case

tions in allo-SCT recipients with myocarditis.

Conclusion

Although the pathophysiology, including the role of cardiotropic viruses, of myocarditis following allo-SCT is unclear, establishing its etiology may be necessary for management. However, we were unable to exclude the possibility of viral myocarditis in our patient. Considering the reversibility of all abnormalities after corticosteroid therapy, an allogeneic immune reaction was suspected to have played a central role in the myocarditis. It is important for physicians to be aware of the possibility of myocardium damage due to allogeneic immune reactions, as such damage may be reversible with immunosuppressive therapy.

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

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