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Fulminant Myocarditis after Allogeneic Bone Marrow Transplantation: Successful Cytomegalovirus Therapy and Mechanical Circulatory Support for Bridge to Recovery

Acute myocarditis is defined as an inflammatory disease of cardiac muscle that may be identified by clinical or histopathologic criteria [1], and this disorder frequently causes left ventricular (LV) dysfunction. The clinical manifestations of this disorder vary greatly from asymptomatic to fulminant fashion, including severe cardiogenic shock, fatal arrhythmia, and acute heart failure [2]. In the setting of fulminant myocarditis [3], one or more mechanical circulatory support devices, such as intraaortic balloon pump (IABP), percutaneous cardiopulmonary support (PCPS), or an LV assist device in combination with inotropic agents may serve as a bridge to myocardial recovery [2]. Here we describe a case of presumed fulminant cytomegalovirus (CMV) myocarditis in a patient receiving allogeneic bone marrow transplantation (BMT), which was successfully managed with antiviral therapy and mechanical circulatory support.

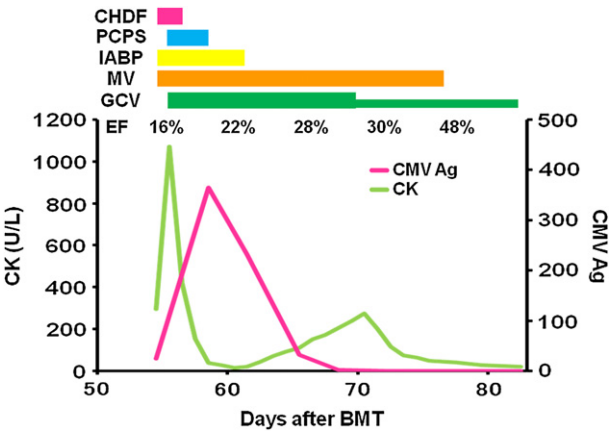

Figure 1. Clinical course and change of cytomegalovirus antigenemia after the onset of presumed fulminant cytomegalovirus myocarditis. Abbreviations: PCPS, percutaneous cardiopulmonary support; IABP, intraaortic balloon pump; MV, mechanical ventilation; CHDF, continuous hemodiafiltration; GCV, ganciclovir; EF, ejection fraction; CMV Ag, cytomegalovirus antigenemia; CK, creatine kinase; BMT, bone marrow transplantation.

A 67-year-old Japanese woman, without previous significant medical history, underwent BMT for acute myelogenous leukemia (AML) with myelodysplastic syndrome (MDS)-related changes from a human leukocyte antigen (HLA)-matched sibling donor. A pretransplant echocardiography showed normal LV function with an ejection fraction (EF) of >60%. CMV antibodies in both donor and recipient were seropositive. The conditioning regimen was reduced-intensity conditioning (RIC) containing fludarabine (Flu), melphalan (Mel), and total body irradiation (TBI); graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (CsA) and short-term methotrexate (MTX). Prophylaxis against viral infection was performed with acyclovir, and CMV pp65 antigenemia was monitored weekly as a guide for preemptive therapy. Engraftment was achieved on day +23 posttransplantation and complete hematologic and cytogenetic remission was confirmed on day +28. As she developed acute GVHD (aGVHD) grade II with skin involvement, methylprednisolone (mPSL) was given from day +49. Five days after the initiation of mPSL, she suddenly developed generalized seizure, deterioration of consciousness and high-grade fever, accompanied by an abrupt drop in blood pressure. Blood tests showed liver injury with elevation of aspartate amino transferase (348 IU/L), alanine amino transferase (120 IU/L), and lactate dehydrogenase (1456 IU/L), as well as cardiac damage such as elevation of creatine kinase 262 U/L (isoform CK-MB 57 U/L). A chest X-ray demonstrated cardiomegaly, massive pulmonary congestion, and bilateral pleural effusion. An ECG showed no site-specific ST-segment alteration, and echocardiography showed markedly impaired LV function (EF, 16%). Magnetic resonance imaging (MRI) of the brain showed high-intensity areas in the bilateral amygdala and pulvinar on the T1-weighted and fluid attenuated inversion recovery image, suggesting limbic encephalitis. As coronary angiography showed no coronary artery stenosis to explain the severe impairment of LV systolic function, fulminant myocarditis complicated with hepatitis and encephalitis was thus suspected. Because of refractory cardiogenic shock against medical treatment accompanied with persistent ventricular tachycardia, mechanical cardiopulmonary support in combination with IABP, PCPS, mechanical ventilation (MV), and continuous hemodiafiltration had to be initiated for the patient. The next day, as CMV pp65 antigenemia was found to be increased (25 positive cells in 2 slides). As systemic fulminant CMV infection was strongly suspected, antiviral therapy with ganciclovir at a dose

of 5 mg/kg twice per day and i.v. immunoglobulin (5 g/day for 3 days) was started. Blood culture was negative for any pathogens. Serologic tests for autoimmune diseases and fungal antigen tests as well as viruses, including echovirus, coxsackie virus, and human immunodeficiency virus (HIV), were all negative. Serologic tests for toxoplasmosis only indicated past infection. Similarly, quantitative polymerase chain reaction (PCR) in blood for herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), adenovirus, human herpes virus 6, parvovirus B19, and hepatitis B and C virus were all negative. On the contrary, CMV PCR was strongly positive (7000 copy/mL). Thus, consistent with the result of CMV pp65 antigenemia, CMV was diagnosed as the main pathogen of fulminant myocarditis. Because administration of ganciclovir was started, her general condition dramatically improved, CMV antigenemia decreased to negative value after the transient increase (peak, 365 positive cells in 2 slides), and all of mechanical cardiopulmonary support devices were successfully removed at 2 weeks after their initiation (Figure 1). Five months after transplantation, she remains in complete remission, without evidence of heart failure or cardiogenic shock.

CMV infection is a major cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). Although CMV is a common pathogen of myocarditis in heart transplant recipients [4], there were few reports on this disease after allogeneic HSCT. In this case, she developed presumed fulminant CMV myocarditis after allogeneic BMT, and was successfully treated with antiviral therapy and mechanical circulatory support. Fulminant myocarditis is characterized by an acute onset of severe hemodynamic instability, and has better long-term prognosis than patients with nonfulminant myocarditis if recognized promptly and successfully managed with appropriate supportive care with inotropes or mechanical circulatory support [3]. Thus, initiation of mechanical circulatory support should be useful as a bridge to recovery for the treatment of fulminant myocarditis even in allogeneic HSCT recipients. Considering the efficacy of antiviral therapy, CMV myocarditis should be taken into account when a patient develops a sudden onset of acute heart failure or cardiogenic shock after allogeneic BMT.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

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Biol Blood Marrow Transplant 16: 129-130 (2010)

doi:10.1016/j.bbmt.2009.05.008

Chromosomally Integrated Human Herpesvirus 6: Transmission via Cord Blood-Derived Unrelated Hematopoietic Stem Cell Transplantation

In 1997, Daibata et al. [1] highlighted the remarkable chromosomal integration of human herpesvirus 6 (HHV6) DNA. We identified a unique case of chromosomally integrated HHV6 (CI-HHV6) after uncomplicated successful unrelated cord blood stem cell transplantation (CBT).

A 1.8-year-old boy with mucopolysaccharidosis type I (Hurler phenotype) was referred for CBT and received a myeloablative (MA) conditioning regimen (busulfan [Bu] 480 mg/m^2, cyclophosphomide [Cy] 200 mg/kg), including serotherapy with thymoglobulin (Genzyme Corporation, Cambridge, MA). Subsequently, a total of 1.5×10^5 CD34$^+$ and 2.5×10^7 nucleated cells/kg of the recipient bodyweight were infused. As graft-versus-host disease (GVHD) prophylaxis, cyclosporine A (CsA; dose is based on plasma