Influenza-induced Rhabdomyolysis after Autologous Peripheral Blood Stem Cell Transplantation for Malignant Lymphoma

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Abstract

We report influenza-induced rhabdomyolysis and congestive heart failure after high-dose therapy and hematopoietic stem cell transplantation for malignant lymphoma. Four months after autologous peripheral blood stem cell transplantation for the treatment of malignant lymphoma, a 65-year-old Japanese man developed acute congestive heart failure requiring artificial ventilation and rhabdomyolysis. Since influenza A virus was documented from his nasal cavity, he was diagnosed as rhabdomyolysis and congestive heart failure induced by influenza A infection. Neuraminidase inhibitor (oseltamivir 150 mg/day for 5 days) was administrated, and heart failure and respiratory status were improved. Our experience suggests that early treatment with neuraminidase inhibitor may improve the clinical outcome of influenza-induced rhabdomyolysis and congestive heart failure.

Case Report

A 65-year-old man, who was diagnosed as angioimmunoblastic T-cell lymphoma at stage IVB with international prognostic index 4, received 3 courses of CHOP therapy (adriamycin 50 mg/m², vincristine 2 mg/body, cyclophosphamide 750 mg/m², prednisolone 100 mg/body×5 days) between May and July 2001. In August 2001, peripheral blood stem cell harvest after high-dose etoposide (500 mg/m²x3 days) followed by granulocyte colony-stimulating factor (G-CSF) was done yielding 4.5×10⁶ CD34⁺ cells/kg. Then, another 3 courses of CHOP were administered. At that time, the cumulative dose of adriamycin was 300 mg/m², and transthoracic echocardiography (TTE) showed a normal left ventricular ejection function of 60%. On November 9, autologous PBSCT was performed in his first complete remission. A pre-transplant conditioning regimen consisted of ranimustine 200 mg/m²/day on day -8 and day -3, carbo-
platin 300 mg/m²/day from day –7 to day –4, etoposide 500 mg/m²/day from day –6 to day –4, and cyclophosphamide 50 mg/kg/day on day –3 and day –2. His post-transplant course was uneventful, and he was discharged on December 17, 2001. Following several preceding days of sore throat and low-grade fever, he suddenly developed dyspnea and orthopnea, and was admitted to our hospital on January 5, 2002. On examination, his body temperature was 38.0°C, blood pressure 102/40 mmHg, and heart rate 136/min. TTE revealed a reduced left ventricular ejection fraction of 32%. He was diagnosed as acute congestive heart failure, and recovered with the use of artificial ventilation and furosemide. No specific cause of his heart failure could be identified at that time. On January 23, TTE showed improved left ejection fraction of 61%. He was discharged on January 30. On March 6, 2002, he first complained of productive cough, and rapidly developed dyspnea and orthopnea. He was admitted again to our hospital on March 7 by ambulance. On examination, his body temperature was 38.8°C, blood pressure 168/100 mmHg, and significant tachycardia (heart rate 190/min) and tachypnea (respiratory rate 32/min) were recognized. His perspiration was remarkable, and edema was found in the lower extremities. Coarse and fine crackles were present at bilateral lung fields. Tachypnea and dyspnea were not improved despite the fact that oxygen supply, and tracheal intubation supported by ventilator was performed. A chest X-ray (Fig. 1A) revealed venous shadows at the pulmonary hilus and interstitial shadows in the lower lung fields. Laboratory tests showed normal levels of serum aspartate aminotransferase (AST) 29 U/l (normal 13–33 U/l), alanine aminotransferase (ALT) 8 U/l (normal 6–30 U/l), and creatinine phosphokinase (CK) 249 U/l (normal 62–287 U/l), and a slight increase of lactate dehydrogenase (LDH) 351 U/l (normal 119–229 U/l). TTE revealed a reduced left ventricular ejection fraction at 25%. The diagnosis of acute congestive heart failure was made, and administration of furosemide and dopamine was started. In an attempt to prevent opportunistic infections under the post-transplant immunodeficiency state, intravenous antibiotics and γ-globulin were administered. On the second hospital day, influenza A virus antigen was documented from his nasal cavity by influenza A, B, quick detection kit (Denka Seiken, Co., Ltd., Tokyo, Japan). Chest CT scan did not disclose interstitial pneumonia, and influenza pneumonia was denied. Neuraminidase inhibitor (oseltamivir 150 mg/day for 7 days) was administered via a gastric tube. On the same day, serum levels of skeletal muscle-related enzymes were elevated; AST 104 U/l, LDH 681 U/l (LDH1: 20.1%, LDH2: 29.6%, LDH3: 26.0%, LDH4: 13.6%, LDH5: 10.7%), CK 1,279 U/l (CK-MB 23 U/l), myoglobin 980 ng/ml (<90 ng/ml), and aldolase 12.7 IU/l (1.7-5.7 IU/l). The urine level of myoglobin was elevated at 760 ng/ml (<10 ng/ml). The patient did not complain of myalgia or muscle weakness, and denied alcohol drinking, drug abuse, trauma, excessive exercise, or convulsion. Thus we estimated that rhabdomyosis and congestive heart failure were induced by influenza A virus infection. To prevent acute renal failure, the patient was given forced diuresis and urine alkalinization. Heart failure and respiratory status were improved gradually, and he was extubated on the third hospital day (Fig. 2). Abnormal shadows on
Influenza and Rhabdomyolysis in a HSCT Patient

Neuraminidase inhibitor

γ-globulin
Dopamine
Diuretics

CRP (mg/dl)

CPK (IU/l)

Mechanical ventilator

O₂ 5 l
2 l

Figure 2. Clinical course.

Discussion

During the period of immunodeficiency following HSCT, patients are at an increased risk of various types of viral infections. According to the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation, the frequency of documented respiratory virus infections was 3.5% among 819 allogeneic and 0.4% among 1154 autologous HSCT patients, the frequency of lower respiratory tract infections was 2.1% among allogeneic and 0.2% among autologous HSCT patients, and the mortality within 28 days from diagnosis of a respiratory viral infection was 1.1% among allogeneic HSCT while no autologous HSCT patient died. The deaths of five patients (0.6%) were directly attributed to respiratory virus infections (three RSV; two influenza A) (6). Thus, among HSCT patients, community-acquired respiratory virus infections such as RS virus and influenza virus are associated with morbidity and mortality. The availability of an influenza diagnostic kit has made a rapid diagnosis possible, and we can use influenza virus-specific antiviral treatment with amantadine or neuraminidase inhibitors such as zanamivir and oseltamivir (2, 3). Therefore, the possibility of an influenza infection should be considered for unexplained or sudden-onset organ dysfunction in HSCT patients.

Rhabdomyolysis is reported to be associated with several virus infections including influenza virus (7, 8), Epstein-Barr virus (9), herpes simplex virus (10), adenovirus (11), enterovirus (12), parainfluenza virus (13), cytomegalovirus (14), coxsakie virus (15), human immunodeficiency virus (16), varicella-zoster virus (17), and measles virus (18). Virus-associated rhabdomyolisis is rare, and accounts for 3–5% of rhabdomyolysis cases (1). Myalgia and arthralgia are common in influenza, but the degree of muscle damage is variable. Morgensen claimed that muscle tenderness is an important feature to distinguish myositis from simple myalgia in influenza patients (7). However, cases of rhabdomyolysis without muscle tenderness developing acute renal failure have been reported (12). Muscle tenderness or muscle swelling was absent in our patient.

The present patient had two episodes of congestive heart failure within 3 months after autologous PBSCT. The cumulative cardiotoxicities of CHOP and high-dose chemotherapy might play a some role in his congestive heart failure. In the first episode, we could not identify specific causes. In the second episode, our patient had influenza A infection-

chest X-ray also disappeared (Fig. 1B). On March 13, TTE showed an improved left ejection fraction of 42%. On March 25, he was discharged without renal dysfunction.
induced rhabdomyolysis and congestive heart failure. Early treatment with a neuraminidase inhibitor seemed to be effective with his prompt clinical improvement. Johny et al described a successful treatment with the neuraminidase inhibitor, zanamivir, in seven patients with influenza post allograft (3). However, the natural history of influenza infection post HSCT is highly variable, and it is difficult to determine the real efficacy of this anti-viral specific therapy.

Rhabdomyolysis in our patient was cured without deterioration of his renal function. Early recognition of this rare complication of influenza and vigorous treatment including forced diuresis and urine alkalinization might have contributed to the good treatment outcome.

In conclusion, we present a case of influenza-induced rhabdomyolysis and congestive heart failure following autologous PBSCT for malignant lymphoma. Early treatment with a neuraminidase inhibitor succeeded in producing the good treatment outcome. The role of neuraminidase inhibitors in HSCT patients developing influenza infection warrants further investigation.

References