CASE REPORT

Rhabdomyolysis After Allogeneic Hematopoietic Stem Cell Transplantation

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Dear Editor:

Rhabdomyolysis is a condition characterized by rapid breakdown of damaged skeletal muscle tissue and release of intracellular myocyte contents such as myoglobin, creatine kinase, and other small molecules into the circulation. Muscle damage may be caused by many factors such as crush injury, strenuous exercise, medications, drug abuse, ischemia, metabolic disorders, extreme temperature and infections.

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is effective for treatment of hematologic malignancies. There are many factors that can affect prognosis. Rhabdomyolysis is an unusual complication of HSCT. In this case report, we present a female patient who developed rhabdomyolysis after Allo-HSCT.

A 41-year-old woman was admitted to our hospital in November 2007 because of fatigue, chills, body ache, and a palpable abdominal mass. White blood cell (WBC) count was $192.8 \times 10^9/L$, hemoglobin level was 92 g/L, platelet count was $501 \times 10^9/L$. Abdominal Doppler ultrasound showed splenomegaly, and myelogram indicated chronic myelocytic leukemia (CML). Also, gene detection showed the presence of BCR/ABL. Treatment with hydroxyurea reduced WBC count and the patient wasn't treated with Imatinib. The WBC and platelet count were decreased.

She was readmitted in February 18, 2008 for Allo-HSCT with her HLA-identical brother as donor. Upon admission, myelogram showed remission of CML. Right jugular

venous access catheters were placed. Body temperature was elevated at 38.5 °C before conditioning. Antibiotics were used to treat infection. The conditioning regimen included busulfan 0.8 mg/kg every 6 h for 4 days, and cyclophosphamide 60 mg/kg once a day for 2 days. Cyclosporine was administered intravenously at a dose of 2.5 mg/kg/day for graft-versus-host disease (GVHD) prophylaxis. This dosage was continued until 2 weeks after transplantation, and was then increased to 5 mg/kg/day orally. She underwent HSCT on March 7, 2008. Methotrexate and mycophenolate mofetil were administered to prevent GVHD. On the 8th post-transplant day, the patient developed a fever. Treatment for infection was started with imipenem + cilastatin and norvancomycin. On the 14th post-transplant day, WBC count was $8.5 \times 10^9/L$, hemoglobin level was 88 g/L, and platelet count was $86 \times 10^9/L$. On the 17th post-transplant day, the density of cyclosporine in the blood was high at 645.8 ng/ml. Dosage was then reduced to 2 mg/kg/day. Gross hematuria was noted on the 27th post-transplant day. The patient was diagnosed with late-onset hemorrhagic cystitis, and was treated with hydration, alkalization of urine, and antibiotics. Serum potassium (K^+) level was 2.9 mmol/L (reference range, 3.5–5.3 mmol/L), and potassium was then administered. She presented with tetany, and calcium gluconate was administered to treat hypocalcemia. Diarrhea was noted on the 38th post-transplant day that progressed to green liquid stools accompanied by a fever with a body temperature of 39.1 °C on the 41st post-transplant day. C-reactive protein level was 97.70 mg/L. Fungal infection was considered, and patient was administered itraconazole. She was diagnosed with acute GVHD and treated with methylprednisolone 80 mg/day for 5 days. The dose was then gradually tapered off, and the immunosuppressant was switched to FK506 binding

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protein. On the 45th post-transplant day, the detection of Cytomegalovirus was negative. She developed anasarca and muscle tenderness on the 55th post-transplant day. Blood examination revealed the following: myoglobin 6255 ng/ml (80–85 ng/ml), creatine kinase 1614 µg/L (25–200 µg/L), aldolase 51.4 µg/L (0–10 µg/L), serum K⁺ 5.7 mmol/L (3.5–5.3 mmol/L), serum sodium 133.4 mmol/L (135–145 mmol/L), chloride 112.5 mmol/L (96–108 mmol/L), bicarbonate 17 mmol/L (22–32 mmol/L), albumin 26 g/L (35–55 g/L), alanine transaminase 47 µg/L (0–40 µg/L), and aspartate aminotransferase 73 µg/L (0–40 µg/L). Muscle biopsy indicated loss of striated muscle with necrosis and proliferation of myofascial cells and infiltration of inflammatory cells. Based on the biopsy result, the patient was diagnosed with rhabdomyolysis. The condition deteriorated rapidly. On May 16, 2008, she experienced dyspnea and massive ascites. Her condition deteriorated and she died of respiratory failure 11 days later, on May 27, 2008.

We report a case of rhabdomyolysis associated with Allo-HSCT. The cause of rhabdomyolysis can be multifactorial.

We believe that the pathogenesis for rhabdomyolysis in this patient is varied. One cause may have been the use of various drugs such as cyclosporine and methylprednisolone. Cyclosporine is a lipophilic endecapeptide derived from a fungus that binds to cyclophilin. Volin et al. [1] have found that an overdose of cyclosporine could induce rhabdomyolysis. To date, only few cases of cyclosporine-induced myopathy have been reported in the literature. In the majority of cases, creatine kinase level was high and biopsies showed fiber atrophy. Cyclosporine also affects the mitochondrial potential and can cause mitochondrial damage [2]. Steroids are also known to increase predisposition to rhabdomyolysis and creatine kinase level elevation. Nava et al. [3] reported acute respiratory and skeletal muscle weakness after a short course of methylprednisolone for acute lung rejection following transplantation. In acute steroid myopathy, weakness is generalized, with severe respiratory and limb muscle weakness. Marked elevation of creatine kinase level can appear. Muscle biopsy shows widespread atrophy of muscle fibers, excess sarcoplasmic glycogen granules, and myofibril disorganization with selective loss of myosin filaments [2].

Rhabdomyolysis has been described in various infections ranging from localized muscle infections with erythema, edema, and tenderness to sepsis without direct muscle infection [4]. Possible mechanisms for the development of rhabdomyolysis include dehydration, toxin release, associated fever, and direct bacterial invasion of muscle [4]. In this case, the patient had localized infection at the site of right jugular venous access catheter

placement. She also had a fever prior to stem cell transplantation. Fever recurred after transplant with an elevated C-reactive protein level and she also has a diarrhea. Immunosuppression and leukocytopenia reduced the ability to resist infection with bacteria, fungi, and viruses. Even though blood culture results or other detection results were negative, we think that infection played a role in the development of rhabdomyolysis.

Metabolic disorders may have been another cause of rhabdomyolysis. Hypokalemia has been reported in the development of rhabdomyolysis [5–8]. After allogeneic hematopoietic stem cell transplantation, the patient developed metabolic disorder manifested by hypokalemia, hypocalcemia, and hypoproteinemia. There is no evidence in the literature that links metabolic disorders, except for hypokalemia, with rhabdomyolysis. However, we believe that all of these metabolic disorders interact and potentially contribute to the development of this condition.

Rhabdomyolysis is a rare complication of HSCT [1, 9]. Severe rhabdomyolysis as a complication of high-dose chemotherapy has also been described [10]. Although the relationship between rhabdomyolysis and respiratory failure is not clear, rhabdomyolysis following Allo-HSCT may be severe and lead to respiratory failure. During therapy for hematologic malignancies, patients should be closely monitored for rhabdomyolysis.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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